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ATDEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES

ADVISORY COMMITTEE

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C O N T E N T S

P R O C E E D I N G S

Opening and Administrative Remarks

DR. FREAS: Good morning. I am Bill Freas and I would like to welcome you to this, the second day, of the meeting of the meeting of the Transmissible Spongiform Encephalopathies Advisory Committee. Today's session will be open to the public, with the possible exception of a short closed session after lunch if needed to present trade secret and proprietary information. That will be clarified as we go along through the morning.

The conflict of interest statement that was read into the public record yesterday morning for this meeting pertains to today as well, and will not be re-read into the record.

For today's meeting, all the members at the table are voting members. I would now like to go around the table and introduce to you the members seated at the head table. I will be starting on the audience's right-hand side of the room and I will ask the members to raise their hand so the audience can identify them.

At the end of the table is Dr. Linda Detwiler, Senior Staff Veterinarian, US Department of Agriculture. Next is Dr. Raymond Roos, Chairman, Department of Neurology at the University of Chicago. Next is Dr. Gilbert White,

Professor, Department of Medicine, University of North Carolina. Next is Miss Barbara Harrell, our Consumer Representative, Director, Division of Minority Health, State of Alabama, Department of Public Health. The empty seat will soon be filled, here on the corner, by Dr. Edmund Tramont, Professor of Medicine, Medical Biotech Center, University of Maryland.

Coming around the corner of the table is Mr. Faitek, a consumer advocate on this Committee, from San Diego, California. Next is Dr. Sindey Wolfe, Director, Public Citizens Health Research Group, Washington, D.C. Next is our Chairman, Dr. Paul Brown, Medical Director, Laboratory of Central Nervous System Studies, National Institute of Neurological Disorders and Stroke. Next is our Nobel Laureate, Dr. Stanley Prusiner, Professor of Neurology, University of California School of Medicine. Next is Dr. Lawrence Lessin, Medical Director, Washington Cancer Institute. Next is Dr. Lawrence Schonberger, Assistant Director of Public Health, Division of Viral and Rickettsial Diseases, Centers for Disease Control. Next is Dr. William Hueston, Associate Dean, Virginia-Maryland Regional College of Veterinary Medicine.

Three members are not with us this morning. They are Dr. David Hoel, Dr. Katherine O'Rourke and Dr. Karen

Hsiao.

Dr. Brown, I would like to turn the meeting over to you.

DR. BROWN: And we have a full day of education today, both for us and any of the public that has joined us. So we will proceed apace. The session will be introduced by Dr. Kathryn Zoon, who is the Director, Center for Biologics Evaluation and Research at the FDA. Dr. Zoon?

Introductory Comments

DR. ZOON: Thank you, Dr. Brown. Good morning, everyone. It is a pleasure to be here this morning to open this day's proceedings of the TSEAC Committee, and I would like to welcome the Committee again personally and offer my personal congratulations to Dr. Prusiner. I would also like to welcome our expert speakers today, as well as invited guests and attendees from the public to hear this very important discussion.

In looking at the topic today, I want to make sure that all interested parties understand that there is an important role for each of you in our advisory committee meetings. In our Federal Register notices we announce the pending advisory committee meetings and we solicit written comments. We also provide time for comments from the floor in the open public hearing, and the Chair has the discretion

to recognize public comments during the committee discussions.

We also welcome written comments from the public after the meetings. It is very important that the members of the advisory committees and the representatives of the FDA hear the opinions of the responsible and concerned people with various points of view.

Today we have asked the TSEAC Advisory Committee to consider an issue of great importance for several FDA centers. This Committee has been asked to consider actions appropriate for the FDA to take concerning TSE-implicated secondary products. These secondary products are those products which, before they were withdrawn, a TSE-implicated blood or plasma derivative was added as an excipient or an inactive additive, or was used as a reagent in the manufacturing process.

In addressing the issue of the FDA policy concerning TSE-implicated secondary products, we have requested a brief public presentation of the most recent information relevant to FDA's general policy on TSE and the risk assessment of blood and blood products as it relates to these agents. We have generally accepted assurances that the risk to recipients from exposure to a TSE-implicated blood and blood product is hypothetical for there have been

no definitive cases of CJD attributable to the receipt of infected blood.

We are aware that FDA's current conservative policy requesting, as a precautionary measure, the withdrawal TSE-implicated blood components and derivatives is based on incomplete science. However, in saying that, we have not asked for today's general review of TSE and blood safety in order to propose major revisions to our current blood policy. FDA's interim policy recently revised, on December 11, 1996, was made stringent both to reflect current scientific uncertainty and to maintain public confidence in the safety of life-sustaining blood products for which there are no substitutes by taking feasible steps to reduce the likelihood of contamination with a TSE agent.

FDA's general policy on blood and TSE will be reexamined at a public meeting of the Public Health Service Advisory Committee on Blood Safety and Availability, which is expected to take place sometime next year. Having said that, of course, we would welcome any comments from our TSE Advisory Committee and the public on these issues, as well as the issues at hand today.

But the main issue today that we wish the Committee to consider is the general issue of TSE and blood products because of the implications that they have on the

safety of secondary products. In particular, we need your advice regarding if the risk of transmitting CJD by exposure to blood and blood products themselves is remote and hypothetical, then what is the risk posed by some of the secondary products made using that blood product? Probably yes and maybe even perhaps negligible.

Immediately after we hear preliminary public comments, speakers from CBER's three offices regulating such products, the Office of Blood, Vaccine and Therapeutics Research and Review, and the speaker from our Office of Compliance with summarize the history of FDA regulatory activities concerning blood, blood components and plasma derivatives from subjects subsequently diagnosed with Creutzfeldt-Jakob disease, or recognize that increased risk of TSE. We will describe some of the outcomes that FDA policy has had for the regulation of secondary products manufactured using blood products that were subsequently withdrawn.

Representatives of the pharmaceutical industry and plasma fractionators will describe the effects of the withdrawal on the manufacture and the supply of their products, and share their view on these issues.

We will then hear a summary of experimental research investigating the potential infectivity of blood

and the possible effects of fractionating on the distribution of TSE agents in blood, followed by a series of epidemiological studies addressing the risk of transmitting TSE to recipients.

Specific questions will then be presented to the TSE Advisory Committee for discussion. Advice will be solicited from the members. They will be asked for their opinions regarding the safety of TSE-implicated secondary products and the appropriate use, if any, of TSE-implicated plasma derivatives, first, as excipient and, second, as reagents used in the manufacturing process.

Again, I am grateful to the members of the Food and Drug Administration's TSE Advisory Committee, and all of you who have come to help us today. Let me particularly thank Dr. Paul Brown, who has assumed the difficult task of chairing this Committee. We look forward to your informative presentations, frank discussions, thoughtful deliberations and well-considered advice. I wish you all a successful meeting. Thank you.

DR. BROWN: Thank you, Dr. Zoon. We will have an overview now and a description of the charge that we are to address, by Dr. David Asher, who is in an office called the Office of Establishment Licensing and Product Surveillance. David?

Overview and Charge to the Committee

DR. ASHER: Thank you, Dr. Brown.

(Slide)

Yesterday we asked the TSE Advisory Committee to advise us on the safety of human dura mater, a class of product that clearly transmitted CJD. Today we consider a much different issue, one where no adverse event has been attributed to any product in its class but for which the public health implications are great.

The TSE Advisory Committee has been asked to consider actions appropriate for the FDA to take concerning TSE-implicated secondary products, that is, products in which, before it was withdrawn, a TSE-implicated plasma derivative or other TSE-implicated blood product was either added as an excipient, that is, an inactive component of the finished product, usually a stabilizer, or used as a reagent in the manufacturing process. Manufacturing process reagents are intentionally removed at the end of the manufacturing process, but the end product was, of course, in contact with the withdrawn derivative during its manufacture.

I have been asked to give an overview of the issue. Let me begin by stressing, in response to some confusion yesterday, that FDA's policies on TSE and blood

have been communicated to regulated industry and to the public through guidance documents. From today's discussion, I think that some information about guidance documents might be helpful to you to understand how this specific issue arose.

(Slide)

A guidance document is an advisory opinion that "represents the Agency's current thinking on a certain subject." The document does not bind the FDA or the public and alternate approaches may be used if they satisfy regulatory requirements. Guidance documents interpret statutes and regulations so that regulatory decisions will be consistent from reviewer to reviewer and predictable from day to day.

Although guidance documents do not bind the public and do not legally bind the FDA, they do serve to constrain the decisions of reviewers to some degree. FDA's decision makers will take steps to ensure that their staff do not deviate from guidance documents without appropriate justification, and without first obtaining concurrence from a supervisor.

(Slide)

Failure to follow guidance is not violative. There are no sanctions imposed by the government, unless the

underlying statute or regulation is violated. But companies do have incentives to follow FDA guidance. First, failure to do so may affect liability, and then the guidance may come to be accepted as good manufacturing practice. By the way, FDA articles, speeches, like the ones you are hearing today, are not guidance. We hope they are helpful but they are not authoritative guidance in the ordinary sense of the word. Regulations, unlike guidance documents, are binding both on the FDA and the public. But the FDA must, with limited exceptions, follow the so-called notice and comment rule-making process, negotiated rule-making. Negotiated rule-making is very labor intensive and it may take years to complete.

(Slide)

Recently the FDA has formalized the process of developing and issuing guidance to make it more like negotiated rule-making. Level 1 guidance represents a significant change in FDA policy, or might be novel, controversial or raise complex issues. FDA will ordinarily solicit public input prior to implementation of Level 1 guidance. For example, the public will be notified; comments will be solicited; and advisory committees may be involved where appropriate. That is really what we did yesterday and are doing today, and there are exceptions to

that, of course, where there are public health emergencies, court orders or executive orders.

(Slide)

Just for your information, Level 2 guidance is used for less significant recommendations to explain policy that is not changing, that sort of thing.

(Slide)

Of course, the FDA does not have, and I am quoting, unlimited resources to dedicated to the development of guidance documents, and if negotiated rule-making procedures are followed very few guidance documents will be issued, and only after a long delay. In the interim regulatory decisions must still be made.

You are all aware of the many recalls of blood and derivatives over recent years, and Mark Weinstein will review that for you. Mike Dubinsky will tell you about related issues of compliance. I will just touch on the FDA's general blood policy.

(Slide)

In 1955, an interim policy was issued on TSEs and blood safety. It placed great weight on maintaining public confidence in the safety of the blood supply and of blood products.

I just might add as an anecdote, loss of public

confidence in the safety of blood and blood products itself has important health consequences. A couple of weeks ago I was called by a mother whose child had been exposed to a bat. The mother refused treatment for the child with rabies immune globulin because of fear that it might transmit CJD, although she accepted the post-exposure vaccination. Apparently, the fear of CJD outweighed the fear of rabies in that family. She did accept post-exposure vaccination and was horrified to learn that albumin -- this is not withdrawn albumin; this is just ordinary albumin -- had been used as a stabilizer in the vaccine.

Obviously, public policy should not be made in response to anecdotes like this and every fear cannot be accommodated. I just wanted to make the point that loss of confidence in a product has important public health consequences.

For that reason, FDA has assumed a very conservative position on blood safety, recommending withdrawal and quarantine of CJD-implicated blood and blood products. A possible reinstatement policy was suggested for products that ended up in short supply but manufacturers voluntarily withdrew their products and did not attempt to reinstate for the reason.

(Slide)

As Dr. Zoon has mentioned, on December 11 of last year a memo was issued to all blood and plasma establishments on revised precautionary measures to reduce the possible risk of transmission of CJD by blood and blood products. As you know, the evidence about the infectivity of blood from subjects with CJD, other TSEs or incubating TSEs is conflicting and disputed, and Bob Rohwer may touch on that issue later this morning. Epidemiological studies, as we will hear, have been consistently negative. Experimental studies have not been completely reassuring. I won't be touch on that further.

(Slide)

The memo of December 11 attempted to classify donors by the probability that they were incubating CJD. Listed here is the highest risk to the lowest risk, starting with donors actually diagnosed with a TSE. Of course, after they have there is an absolute certainty that they were incubating CJD. Then donors with an increased risk due to definite familial TSEs; iatrogenic TSE; possibly increased risk of TSE in someone with a single family member because in most of those the family member will have sporadic CJD; and some other classifications.

(Slide)

To quote from that memorandum, as a precaution FDA

recommends that source plasma and plasma derivatives prepared from donors later diagnosed with CJD, and donors who are at increased risk for developing CJD should be quarantined and destroyed. An exception was given in the recommendations for a donor with only one family member with CJD or products intended for manufacturing non-injectable products, although even for those advice was given that they be labeled with a cautionary statement. Finally, a donor with CJD or at risk for CJD, for such donors consignee notification was recommended to permit recipient tracing and notification as medically deemed appropriate. That is, the consignee would decide whether the recipients were to be informed of the remote and hypothetical exposure or not.

(Slide)

The memorandum of December 11 is viewed in the Agency as an interim guidance document, with limited applicability. It was realized that it wouldn't cover every possible circumstance, and that it might become outdated as advances in science and technology occurred.

(Slide)

Here is the FDA problem: A CBER reviewer or a consumer safety officer has been contacted by the representative of a company that was the consignee of a withdrawn CJD-implicated blood product. The company was

notified that the product had been withdrawn after it had already used the withdrawn product in the formulation or manufacture of a secondary product. For example, the manufacturer used the withdrawn plasma derivative as an excipient, a stabilizer, in some injectable biologic; or, it used the withdrawn plasma derivative to supplement medium for cell cultures used to prepare an injectable biologic; or, some other kind of manufacturing process reagent, maybe in a column. The biologics have already been distributed. What does the FDA reviewer think is appropriate for the manufacturer of the secondary product to do with that product?

By the way, this is, not strictly speaking, only a CBER issue. Both CDRH and CBER regulate products that are produced with such derivatives.

(Slide)

The relevant guidance document, most recently the memorandum of December 11, allows for flexibility but its language is fairly explicit. Remember that, as a precaution, plasma derivatives should be quarantined and destroyed, and products intended for further manufacture into non-injectable products should be labeled with a cautionary statement. That is not advice that it is okay to go ahead and use the product to make another product. That

is advice that the product should be destroyed.

Remember again that the front line staff are not to deviate from guidance documents without appropriate justification, and without first obtaining concurrence from a supervisor. Well, those supervisors have been concerned about the issue, just as the reviewers were concerned, and they also felt that additional guidance should be provided.

In November of last year, the CBER office directors discussed an interim policy and decided that the issue was appropriate to present to the TSE Advisory Committee, and that is why we are here.

(Slide)

The interim policy is essentially this. Gerry Donlon, my Office Director, suggested that a decision matrix might help to summarize the policy. At the moment, for secondary products containing a withdrawn excipient, withdrawal is recommended regardless of whether the implicated donor either had TSE or was having increased risk of TSE. Of course, exceptions would be entertained. There seems no logical reason why the same substance used as an active ingredient would pose a different risk from a substance used as an excipient. And secondary products from implicated manufacturing process reagents are being evaluated on a case by case basis.

(Slide)

Again, here is the charge, which I won't bother reading a second time and you should all have copies of it. Let me finish by reviewing the factors that are currently being considered by the FDA in the review of TSE-implicated secondary products, and these are similar to the factors that you discussed in considering the safety of dura mater yesterday.

(Slide)

First, of course, the population to be treated. Some patients with a life-threatening illness and a short life expectancy might justifiably assume a remote and hypothetical risk that might not be reasonable, for instance, for a healthy child with a full life ahead of him or her, to accept.

Second, the dose of the TSE agent potentially contaminating the secondary product. Excipient, of course, as we mentioned differ from active ingredients only in their intended use, not in the amount of the product present.

Manufacturing process reagents -- the reagent is intentionally removed during the process. If it is not successfully removed it constitutes a contaminant. That might pose a low risk unless the agent somehow left the contaminated reagent and went into the final product. We

don't know if that can ever happen.

A donor with a diagnosed TSE, 100% likelihood that he or she was incubating, might be considered a greater risk, although we recognize that in any large plasma donor pool there is likely to be a donor who is destined to get sporadic Creutzfeldt-Jakob disease. Dr. Schonberger talked about the probability in certain age groups being considerably higher than one in a million for the general population.

(Slide)

Manufacturing process -- obviously, a process with one or, better, two inactivating removal steps would be preferred. A process that had been validated in a model that was in the same context as the manufacturing process would provide us with greater assurance than information gleaned from the general scientific literature.

Cells susceptible to infection, if they are used in the preparation of a biologic, would be of special concern. Supply of the products -- of course, the product should be of substantial benefit and no substitute available, or else it probably isn't worth considering.

This proposes a regulatory dilemma because the same product might be considered acceptable when there is a shortage and unacceptable otherwise, and regulators don't

like making that kind of distinction. They like making distinctions based on the product being considered safe or not safe.

(Slide)

The route or other features of administration -- of course, administration into the central nervous system is of greater concern than other injectable uses or implantable ophthalmic uses. Oral administration is of somewhat less concern; intact skin is of less concern. Frequent use or large volumes are of greater concern than intermittent use or single-use, smaller volumes.

Finally, I just want to touch on an issue just to let you know that it is considered, and that is disclosure. We realize that issues of disclosure are controversial where we are dealing with remote and hypothetical risks. We don't expect that controversy to be resolved today. FDA recommends notification of consignees and health care providers, and asks that notification of recipients be considered.

For investigational drugs, we have suggested strongly that disclosure be included in the informed consent document, and that has been done. But FDA, as I understand it, cannot require disclosure of risks that are hypothetical only. Ordinarily, an adverse event is recognized,

attributed to exposure to a product, and that has to be disclosed but not every hypothetical risk that one can imagine.

So unless you specifically want to hear the questions which will be read later by Gene Murano, and you have them in front of you, I will stop here. The questions will be devoted to the safety of excipient of secondary products in which a TSE-withdrawn product was used as an excipient, and those in which it was used as a manufacturing process reagent. I think I have run over. Thank you.

DR. BROWN: Thank you, Dr. Asher. We now have a period when the public can let us know what they think about these issues, and Bill Freas will direct this open public hearing.

DR. FREAS: As Dr. Zoon said, we welcome comments from members of the public at these advisory committee meetings. I have received, in response to the Federal Register announcement for this meeting, four requests to present before the Advisory Committee. The first request was received from Patricia Ewanitz. Patrician, would you please come to the microphone, and while you are coming to the microphone, we ask that all speakers, in fairness of interest, address any current or previous financial involvement they may have with any firm whose product they

may wish to comment upon. Patricia?

Open Public Hearing

Patricia Ewanitz

MS. EWANITZ: My name is Patricia Ewanitz. I am here today to lobby for changes in dealing with Creutzfeldt-Jakob disease. I have no affiliation with FDA-regulated firms. I was a housewife for 35 years. On January 23, my husband was at work and he suddenly couldn't spell or sign his name. He made an appointment with an internist, who referred him to a neurologist. His diagnosis was mild stroke. On February 6 he had an MRI, and on February 7 and ultrasound, both of which were normal. On March 4 he had a rapid CT heart scan. There was no evidence of neck or heart artery plaque.

His speech started to become impaired. The neurologist told him his speech would return to normal, and he should go home and rest and make an appointment to see him in his office in one week. On March 8 I took him to the hospital emergency room as not only his speech was getting worse, he could not speak full sentences, and his hands started to curl.

In the hospital he was treated for CVA. His symptoms worsened daily. His intravenous medication caused hemorrhaging under the skin. An EEG was performed, which

was abnormal on the left side of his brain. The doctor said he was a puzzlement. I went home and read some medical books and went back to the hospital, and I asked the doctor if he had CJD. From what I had read, his symptoms seemed to match that disease. The doctor told me it was possible. He could have had a slow brain virus. A resident sent his cerebral-spinal fluid to NIH. On March 18 he was sent home. There was nothing else they could do for him. There was no definitive diagnosis.

I told the doctor he was a blood donor. The doctor told me there was nothing I could do about it now. It was not until a couple of months after his death, after I learned more about the disease, I was advised to contact the blood center so they could trace the donated blood. They haven't gotten back to me yet. They are still tracing it.

Doctors have to be educated to recognize the symptoms in order to diagnose this disease so the patient does not have to endure treatments which only product more suffering. Many CJD patients are misdiagnosed. One patient was even diagnosed with conversion reaction disorder and was put under psychiatric care. More funds have to be allotted for research. I have heard statistics that only one in one million persons contracts CJD. I don't care how many victims; one is too much. With more research and better

diagnosis, I believe the victim count would be much higher. There have to be studies done with Alzheimer's patients who, when autopsied, revealed their diagnosis of Alzheimer's disease was actually CJD.

I am glad to see the government is starting to take an active role in this horrible disease. If the Britains, ten years ago, when BSE was discovered had spent the amount of money on research instead of protecting the beef industry, we might be closer to an answer.

CJD has been hampered by the lack of a central registry, and the reluctance of many pathologists and clinicians to handle the patients. A cheap actuary for a large insurance company lists CJD as acute syphilitis. CJD has to be made a reportable disease nationally, not just regionally, in order to obtain realistic statistics.

I have a statement from one of our group members. It reads, "I am a nurse and know from my mother's case that because she did not have an autopsy, her case and five others I have cared for, were not counted as cases because the diagnosis was not confirmed by autopsy. My mother's EEG showed a classic pattern for CJD and her clinical picture was classic. There is no doubt in my mind that my mother, as well as the other cases, were CJD."

How can you say that CDC statistics are correct

when there are many instances like this? There are many others who contact us looking for clinicians and facilities to perform autopsies. One such case had to go to a medical school where a pathologist was a resident in training. He came to the funeral home, 50 miles from the medical school. Families not only have to care for these patients but, while doing so, they have to fight the medical establishment for confirmation by autopsy. This has got to change. If CJD is made a reportable disease an autopsy would be mandatory.

The mental pain of these patients is horrendous. It is constant fear. Could you imagine yourself severely frightened, with a body constantly shaking with tremors, and no way to communicate? There is no solace in sleep as there is no sleep. It is 24 hours of torture for months. I have seen this. My husband was home until the last ten days before his death. Something more has to be done.

A number of CJD victims' families have formed an action group. We are going to actively pursue obtaining further funding, surveillance, and having CJD made a reportable disease.

I also have a statement which I was asked to read from another member of our group. Her name is Liz Armstrong. It says: Dear members and Committee, first allow me to thank you for expressing my concerns regarding

the human version of TSEs, referred to as Creutzfeldt-Jakob disease. I regret that I cannot personally attend this meeting, and appreciate the Committee's permission for my statement to be read allowed.

I am the moderator for a newly formed support, action and discussion group on CJD Voice. In July of this year there were three of us that began sharing information about CJD, and decided to form a group. As of today, there are 40 members in our group, all who are suffering with a family member with CJD or who have already lost someone to this horrific diseases. In just three months, we have 25 times the number of members. These are individuals that have been given at least a probable diagnosis of CJD by a neurologist or a physician, and are seeking knowledge or support. I dare not attempt to speculate on how many families are out there and have not investigated the diagnosis they were given.

This disease, until recently, was not actively monitored in the United States, and now is only monitored in four states or regions. The CDC, except for those areas, does not require CJD to be reported. While I understand reporting is mandated on a state level, the CDC does not have the authority to deem this a nationally quarantinable disease. In order for the FDA to monitor blood-based

products, it would seem imperative that all cases of CJD should be reported to an authoritative agency. By mandating reporting, medical professionals would be more aware of the clinical and pathological symptoms, thereby, eliminating a vast majority of misdiagnosis.

Recent studies have shown that approximately 13% of Alzheimer's cases were found upon autopsy to be CJD. I am personally aware of two cases, possibly three, of CJD in a town with a population of less than 3000. These cases were all within a 10-year span, and none of the victims were related even distantly. I know for a fact that at least one of these cases was not reported to the CDC, even though CJD was listed as the cause of death on the final death certificate.

Putting the numbers against the one per million figures, it would take 90 towns of this size to produce 3 cases in 10 years. Had these cases been reported, the occurrence figures would have fluctuated from year to year. The existence of the four established reporting sites would not, and did not cease these cases in their study. How many others have been missed?

In the April-June, 1997 issue of Emerging Infectious Diseases, Volume 3, No. 2, there is an articled called "Creutzfeldt-Jakob Disease Transmitted in Blood."

Studies have now confirmed blood to be evident as a mode of transportation. Upon my father's death, on May 6, 1996, I began researching CJD. At that time, the Canadian Red Cross had implemented a recall of CJD-tainted blood. This prompted me to contact the American Red Cross as my father had been a life-long donor and had been awarded a "gallon pin" for all his donations.

Other than a brief response to inform me that this matter had been forwarded to a district office, I have received no reply. I have never officially been informed of my impending exclusion from donating blood, nor has the Red Cross nor any other agency inquired as to my blood donation activities.

On Friday, October 3, 1997 the Canadian Red Cross alerted hospitals across the country that up to 100,000 patients may have received CJD-implicated blood products. The donor did not actually have CJD. However, he carries the mutation associated with familial CJD. The donations were made six years ago and all products were expired prior to 1994 and, yet, the Canadian Red Cross recognizes the severity of this issue and has elected to notify recipients.

As a member of our discussion group, I have heard real-life horror stories of CJD victims forced from hospitals, patients strapped down in psych wards,

misdiagnoses ranging from Parkinson's to Alzheimer's, hospital rooms sealed for months after use by a CJD patient, families refused autopsies, funeral homes refusing to accept CJD patients. The stories are endless. The fear surrounding this disease has developed from the lack of knowledge in the majority of the general medical community. While I feel our family was extremely lucky to obtain an autopsy, the facility had no knowledge of requests from NIH for tissue samples from CJD patients.

I understand continuing medical education is not available to include every disease on the current basis, however, this was a Veteran's Hospital, run by the same government that controls NIH. By mandating the reporting of CJD increased control could be established to monitor cases of CJD and, at the same time, it would alert the medical community of the need to continue education regarding CJD. Most members of our group responding to a survey have reported that they were not notified by their attending physician as to requests for samples by NIH, and were also denied autopsy.

At present, several members have a loved one alive and fighting the CJD battle, and have already been told autopsy is not an option. Until government sanctions are in place all hopes of increasing public and medical knowledge

of this disease are stagnant. Without public awareness and continued medical education specifically regarding CJD, funding for research will continue to diminish and misdiagnosis will continue.

I implore you, as an authoritative agency, to mandate procedures to ensure proper reporting and increased research and educational funding. It is only through continuing research of viable information that we can eliminate risks associated with CJD and blood products. Thank you for your time. Respectfully submitted, Mrs. Luce Armstrong.

DR. FREAS: Thank you, Patricia, for your comments and those of Mrs. Armstrong. Our next speaker is Dr. Michael Hansen, from the Consumer's Union. Would you come forward and use the microphone?

Michael Hansen, Ph.D.

DR. HANSEN: Thank you very much. I should also report that I have no connection to any of the regulated industry. I thank the Committee for allowing me to speak today.

Following up on what Patricia said, I would like to start by saying that studies you will hear today from both Dr. Brown and Dr. Rohwer's lab have shown that in animal models the infectious agent is present in various

blood fractions. Because of this, I would like to commend the FDA and the blood industry for taking the preventative step of withdrawing or recalling blood and blood components from donors that are later diagnosed with CJD. However, for this action to be effective we must be able to truly identify all the CJD cases that are out there.

I think, as Patricia has stated, there is some evidence to suggest that CJD rates are being under-reported and that the true numbers could be much greater than one in a million. In fact, CJD can be mistaken for quite a number of diseases, such as Alzheimer's disease, stroke, etc.

A couple of lines of evidence that support this is that in the scientific literature there was a study done at Yale by Manuelidis, et al., that found 6/46, or 13%, of Alzheimer's disease patients turned out, on autopsy, to be confirmed CJD. A study done at Pittsburgh, by Boller, et al., looked at 55 cases of dementia. Most were considered probable or possible Alzheimer's disease. Three of those, or 6%, turned out to be CJD. Both of these are very small studies but they are suggestive, and we have to remember that there are four million cases of Alzheimer's disease out there and hundreds of thousands of cases a year, so even if a small percentage of them are CJD we are talking about much larger numbers.

The second source of information is all anecdotal, but it is the stories from the CJD victims themselves. You have heard some stories from people in CJD Voice. There is actually another CJD support group called the CJD Foundation. A number of these people have been in contact with me and I have talked with at least 15 of these people who have had it in their family. And the stories you hear are all variations on a theme. Usually the initial diagnosis is not CJD, and it is someone in the patient's family who usually has to fight with the doctor to ultimately get the right diagnosis.

You have heard about Patricia's case. There was a case from Los Angeles, a woman who died just this summer, whose son was a stockbroker who called me up and told me his story of his mother's case, which was very rapid onset. Symptoms started on June 5, she was dead by the end of July. He had to have a huge fight with the mother's HMO before they would even permit any neurological testing at all. He said it was quite a big battle but they finally sent out cerebral-spinal fluid to NIH to be tested. It came back positive, and I believe it was confirmed at death.

I heard of another case from Oklahoma where this nurse's mother died last year. She told me that her mother had been diagnosed with rapid onset Alzheimer's. The

daughter, who is a nurse, didn't agree with that and she told me that she was, quote, pig-headed and had to fight with the doctor. In fact, she ultimately had to be the one to arrange to have the spinal tap taken to be sent off to NIH for testing.

These are just a couple of cases. There are a number more. I should also point out that a number of these cases have also given blood. Patricia told you about her case today. I was the person that told her, when she talked to me, that she needed to be notifying the authorities. Liz Anderson, who was supposed to speak today, her parents had donated blood also. I have spoken to a few other people that have. So this is just anecdotal information but it does suggest that the disease is not really being diagnosed and unless there is someone in the family willing to fight that it gets diagnosed, there are all sorts of other things.

So we support the call for making CJD a reportable disease. We also think that studies should be done among Alzheimer's patients or dementia patients using the NIH 14-33 test, of course, in conjunction with clinical histories to get some kind of feeling to see if some small percentage of these four million Alzheimer's cases are, indeed, CJD to see if the problem is much higher than we think it is.

Finally, I would like to end by saying that I would like to suggest one other thing to the Committee. This has to do with a potential trade problem that the U.S. might have. It should be pointed out that the European Commission has passed a regulation that will come into effect starting January 1 of next year, and that is, they are banning the use of what they call SRMs, specified risk materials. At this time that is eyes, brain and spinal cord of cows, sheep and goats that are older than one year, and the spleen from all goats and sheep. Those are SRMs are banned from any use whatsoever. So the context that is important for this Committee is that as of January 1 any pharmaceutical product that wants to be sent into the European Union has got to not come from or be derived from any material containing an SRM.

The U.S. trade representative is calling this what they call the tallow ban and they are threatening action at the World Trade Organization. I would just like to point out that this recommendation that is being implemented in the EC is just a recommendation, number 4, that came out of last year's WHO consultation on TSEs and public health.

I think what the Committee should recommend that FDA do, so that we do not have trade problems with any of our pharmaceutical or blood products, is that we should be

in line with what the European Commission, European Union is doing. They are taking their cautionary principle seriously and I think that the Committee should recommend that the FDA say that no material that goes into any blood or secondary product, or any pharmaceutical product should come from or be derived from any material containing an SRM, a specified risk material.

This is even more important given the fact that the FDA approved the feed rule that has just come into play, which explicitly permits TSE-positive animals to go into the food chain -- well, into the animal food chain, into pet food, and it can go into animal feed as long as it is labeled do not feed cattle and other ruminants. So we have a law that permits known TSE positives. That would mean scrapie-infested sheep, CWD-infected deer. I think evidence has come out in the last couple of months, just last week, the announcement in Britain that new variant CJD is, indeed, linked to BSE. A couple of months before that, the work that came out of the Rocky Mountain Lab of NIH and of The Netherlands demonstrated that both BSE and scrapie appear to be able to convert or recruit normal human prions to the abnormal confirmation. It should be pointed out that scrapie was just as infective as BSE at converting human prions.

Since they now admit that nvCJD is sort of BSE in humans, we have to say that there is a possibility that a similar thing could happen with scrapie. And unlike the European Union, since the U.S. still permits these TSE-positive animals to go into the food supply, I think that the Committee should recommend to the FDA that they follow the lead of the European Commission and say that no pharmaceutical products and no blood or blood products can come from or be derived from any material coming from specified risk materials.

Thank you very much.

DR. FREAS: Thank you, Dr. Hansen. Our last speaker in the open public session is Dr. Donald Tankersley, from Plasma Derivatives Consulting.

Donald Tankersley

MR: TANKERSLEY: Dr. Brown, members of the Committee, my name is Donald Tankersley, and I am presently a consultant for the plasma fractionation industry. I am not being compensated for this presentation in any way.

What I am going to be discussing is the primary products, but I think it should be reasonably clear that the risk for secondary products is tied to the primary products. So I want to discuss what we can learn about the risks of these primary plasma derivatives.

Recipients of a dura mater graft may be at increased risk for developing CJD, as we heard yesterday. In most cases, where the dura comes from a single donor, the lifetime risk in a dura mater recipient would be approximately twice the normal risk. That is, the risk will be the sum of the inherent risk of the recipient in developing sporadic CJD plus the probability that the dura derived from an individual incubating the disease.

Now, if cross-contamination of dura mater from multiple cadavers occurs during the processing, that risk of transmission to a graft recipient might be increased further. For example, if 50 dura were stored in intimate contact, then the recipient's risk of CJD might be increased as much as 50-fold.

Because of this increased risk, on December 11, 1996, CBER recommended that dura mater graft recipients be permanently deferred from donating blood or plasma. Moreover, CBER recommended the quarantine, recall and destruction of all plasma derivatives produced from a pool which included a plasma donation from a dura mater graft recipient. I want to ask this Committee to consider in particular the extent of the increased risk of exposure to CJD incurred by users of plasma derivatives derived from such a pool. Plasma derivatives are prepared from large

pools of plasma, typically comprising donations from 10,000 to 60,000 individuals. This Committee should not need to be reminded again that there has never been an association of CJD with the use of plasma derivatives, even though it is a statistical certainty that many of the plasma pools from which these products are derived include donations from individuals incubating CJD.

I want to present an alternative way of looking at the risk of exposure to CJD by recipients of plasma derivatives. I need to define a few terms.

(Slide)

The risk of exposure, as I am going to be discussing it, is the probability that a given plasma derivative was made from the plasma pool that included a donation from an individual incubating CJD. Now, we don't know the extent of the incubation period, but in recipients of pituitary-derived growth hormone it may be as long as 25 years. We also don't know if blood or plasma is infectious during this entire incubation period. However, the conservative view is taken, namely, that plasma might contain infectivity for 25 years before the appearance of disease symptoms. The incidence rate for sporadic CJD is approximately one case per million individuals per year.

If we assume that plasma may be infectious for 25

years before disease symptoms appear, then one in 40,000 individuals with no other risk factors for CJD will be incubating the disease at any given time. We can use this prevalence to estimate the probability that a plasma pool will contain one or more such donations, using the binomial distribution equation. This is, of course, a function of the number of donors contributing to the pool.

(Slide)

For purposes of illustration I have used an N of 30,000, which is certainly not atypical for plasma derivatives. As shown on this overhead, the probability that a pool of 30,000 plasma donations from normal donors, without known risk factors for CJD -- the probability that this pool will contain at least one unit from a donor incubating the disease is 0.527638 or slightly more than one half.

Now let's consider a case in which the plasma pool includes a unit from a donor who has received a dura mater graft, processed without exposure to other duras. As I think we have discussed, the risk in this case could be as much as twice that of a normal donor if, in fact, the dura had not been inactivated.

So the risk is now 50 millionths rather than 25 millionths, and the probability that a pool will include a

unit from someone incubating the disease is increased to 0.527650. So including a unit of plasma from a dura mater graft recipient increased the likelihood that the pool will contain at least one unit from an individual incubating the disease by a whopping 0.00012, or about 0.0023 percent.

Perhaps a simpler way of looking at this risk of exposure is to consider the dura mater graft recipient as representing a risk equivalent to that of two normal donors. That is, that individual contributes his own inherent risk as well as that of the dura donor. Looked at in this way, the risk of exposure incurred by a recipient of a derivative produced from the plasma of 30,000 donors, one of whom who had a dura mater graft, is exactly the same as that of a product produced from 30,001 donors who are without this additional risk.

Even if the graft had been processed in a manner that allowed cross-contamination with 50 others, the risk of exposure by products produced by the pool would be no more than that of a product derived from the plasma of 30,050 donors.

Are we really to believe that such a minuscule increase in the effective pool size warrants the recall and destruction of valuable products that are more or less in chronic short supply?

Finally, I want to emphasize that the risk of exposure is not the same as the risk of infection. Risk of exposure is simply the likelihood that the product was derived from a pool which included a unit from a donor who might later succumb to the disease if he doesn't die of other causes first. The risk of infection depends upon a number of additional factors which are poorly understood. We may learn more about these today.

Is plasma infectious? If so, what is the level of infectivity and how long before symptoms appear is the plasma infectious? Is infectivity diminished or removed by manufacturing steps? How effectively is CJD transmitted by intravenous or intramuscular routes as compared to intracerebral routes?

These questions need to be answered before the actual risk of CJD transmission of plasma derivatives can be estimated, but this risk is always less than the risk of exposure and, of course, that may well be zero. So I would urge this Committee to recommend that plasma derivatives not be recalled when post-donation information reveals that a plasma donor has received a dura mater graft.

Thank you for your attention.

DR. FREAS: Thank you, Mr. Tankersley. His speech is also in the blue folders that are on the table for the

Committee members.

At this time, is there anyone else in the audience who would like to address the Committee? I see no response so, Dr. Brown, I turn the meeting over to you.

DR. BROWN: The next four speakers are going briefly to go over certain aspects of FDA regulatory activities and regulated products. They will be followed by two speakers from the industry, one from Bayer Corporation and one from the Red Cross. So Dr. Weinstein is the first of the several speakers. He is from the Office of Blood Research and Review of the FDA.

FDA Regulatory Activities Concerning CJD and Human Blood, Blood Components and Plasma Derivatives: Concerns, Actions, Responses, Results

Mark J. Weinstein, Ph.D.

(Slide)

DR. WEINSTEIN: The topic of my presentation will be the FDA regulatory activities concerning CJD and human blood, blood components and plasma derivatives, our concerns, actions, responses and results.

(Slide)

I will first give a brief review of the history of our recommendations, then describe the current status of the

FDA recommendations, and then the effect that these recommendations have had on withdrawal of products. Lastly, I will describe a case study that illustrates FDA's risk assessment process.

(Slide)

Between 1983 and 1994 there were reports of six donors diagnosed with CJD. In this case, in-date material was voluntarily withdrawn.

In November of 1987, the FDA issued a memorandum to blood establishments that called for the deferral of recipients of human growth hormone. This followed a report in the literature that such recipients of human growth hormone could transmit CJD -- or could acquire CJD.

In December of 1993, the FDA issued a memorandum called The Guidance Regarding Post-Donation Information Reports. This memorandum emphasized post-donation reporting and called for more documentation, further investigations and description of withdrawals by blood collection establishments. It also called for increased notification of the FDA and of consignees about withdrawals.

(Slide)

In 1995, this action led to increased numbers of reporting regarding CJD. There were seven reports of individuals diagnosed with CJD and five donors at increased

risk for CJD who had donated to blood pools.

In August of 1995, the FDA issued a memorandum to blood establishments which further defined the population who were at increased risk for CJD. This memorandum gave recommendations about the disposition of products from such donors and recommendations about notifying consignees who received implicated products. I will discuss these recommendations in more depth a little bit later, when reviewing the revision of these documents that was issued in December of 1996, of which Dr. Asher has also given a review.

(Slide)

In 1996, the FDA further initiated a number of forms to develop policy regarding CJD. The FDA sponsored a CJD workshop in January of 1996. There was a Blood Products Advisory Committee update in June of 1996, and TSE Committee meeting in July of 1996.

In October of 1996, the FDA requested that manufacturers add a statement on plasma derivative labeling that would alert recipients to the potential of these products to transmit known and unknown infectious agents despite viral inactivation procedures.

Finally, in December of 1996, FDA issued a memorandum to blood establishments, called, Revised

Precautionary Measures to Reduce the Possible Risk of Transmission of CJD by Blood and Blood Products. I will just briefly review some of the highlights of this document.

(Slide)

The criteria for donor risk assessment for deferral was established and, again, a modification of what had already been issued in August of 1995. Applicant donors were questioned about CJD to assess the potential for risk. That is, did the applicant donor have a family history? Did the applicant donor receive human growth hormone? Had the person received a dura mater transplant?

Familial risk was defined as a person considered to be at increased risk if the person had been told of a family member who had familial risk of CJD, or if the individual knew that the person had two or more family members with CJD.

Donors with relatives with iatrogenic CJD were not considered to be at risk. The category of possible familiar risk was defined if a donor has one affected family member the donor may resume donations if genetic testing is negative for the CJD risk.

(Slide)

The memorandum described the disposition of products that were obtained subsequently from donors who

were identified to either have CJD or to be at risk for CJD. That is, the donor may have given at a previous time and subsequently was identified to be in these categories.

For donors with CJD all products for injections should be destroyed, and consignees notified to destroy the product. For donors at risk for CJD, that is, those that had received the human growth hormone, familial CJD or dura mater recipients, the memorandum requested that the plasma be quarantined and destroyed and that blood components similarly be treated in all cases of increased risk. The exception was unless a donor has only one family member with CJD, in such cases the plasma derivatives may be used from a donor with a history of only one known family member.

(Slide)

The memorandum also outlined that plasma derivatives from at risk donors may be used for further manufacturing into non-injectable products if labeled with cautionary statements, such as biohazard, collected from a donor determined to be at risk for CJD, and so forth. It also outlined a policy of notification, that is, it was recommended that the consignee notification was recommended unless the donor has only one family member with CJD. Also recipient counseling decisions should be based upon the risk-benefit decisions by physicians or caretakers.

(Slide)

I would like to next turn to the effect that these recommendations have had on product withdrawals. This graph shows the numbers of donors who have given blood and have subsequently been identified to have CJD or be at increased risk for CJD. As you see, over the period of time from 1983 to 1994 there were relatively few identified donors who fell into the category of having CJD.

Later on, as our increased awareness of the disease, and the recommendations that were issued by the FDA came into play, there was an increased degree of reporting of these donors. You see that the level, the numbers that actually have CJD have remained relatively constant and are about what one would expect for a donating population of around 12 million donors. We see that we have 10 individuals in 1995 who were identified with actually having CJD.

(Slide)

This slide breaks down the categories further. You can see that, actually, in 1995 there were 9 donors; in 1996 there were 10 donors with CJD. Throughout this period of time you can see an increase in the number of donors who were identified as dura recipients. In fact, in 1997 that accounts for approximately half of the people who were

identified as at risk and caused withdrawal of products. Again, it is very important to note that there are relatively low numbers here. We are only talking about on the order of 30 or 40 individuals in 1997 and, yet, this had a profound effect on withdrawal of product, as we will show you next.

(Slide)

First of all, as you know, a single unit of product may be incorporated into many other units of materials and into pools, and so forth, and a wide range of products are affected: blood, blood components, albumin, immune globulin, clotting factors, and also excipient for drugs, vaccines and in vitro supplements, as outlined in this chart.

These donations have led to a large number of withdrawals, and this chart shows the lots of material that have been withdrawn. Again, you see the increased numbers of time. From 1983 to 1995 240 lots of albumin were withdrawn. But, again, as increased reporting and awareness of the disease occurred, in 1996 and 1997 we have close to the same numbers here, around 200 lots withdrawn of albumin. Again, you can see for all of these numbers that there is an increasing amount of material withdrawn as our awareness increases.

One doesn't get a sense from just lot numbers of what the numbers or the volume of material, the amount of material that is actually implicated in these withdrawals because manufacturers will differ in the size of their lots and in the particular way that they will manufacture material. So these situations may affect one company much more than another depending on how the product is obtained, from volunteer donors or source plasma donors, and how the individual company may pool and process that material, whether there are large pools or small pools, and so forth.

(Slide)

To give you an idea of the amount of material affected by these withdrawals over the period of time, what we have done here is to take the production rate of 1996 for these various products as the denominator and then to calculate what the kilogram or units of material are that were actually withdrawn or were affected by this policy over this period of time.

You can see that for immune globulins, for example, between 5% and 15% of material was withdrawn over the period of 1995 to 1997. For Factor VIII the amount is more on the order of 15% to 20% of plasma derived Factor VIII.

There is a very important caveat to mention here,

that when we talk about withdrawal we are talking about a recommendation that goes to industry that is not audited by the FDA, and the amount of material that is actually returned to the company might be considerably less than what you see here because much of the product will have already been consumed in that time period, from the time that the donor is identified as being at risk or as having CJD. So although these numbers look very large, the actual effect might be somewhat smaller.

On the other hand, for a given company at a particular time there may be a very severe shortage, and I am sure we will hear later on from the Red Cross about the effect of this policy on their product availability. Among other companies, there can be a severe effect and spot shortages for brief periods of time, depending upon whether industry can make up for the shortages that might occur. This may or may not happen for a certain period of time. So we are confronted occasionally, or I should say routinely, by potentials of shortages which are difficult for us to assess.

(Slide)

This just gives a brief description of a case in which we had to evaluate the potential of a TSE-implicated secondary product affecting a marketed product. This is the

so-called transferrin case in which there was indirect exposure to implicated material. In this particular case, transferrin was made from a CJD-implicated pool. The transferrin was used as a growth factor for the production of monoclonal antibodies. The amount of transferrin used was in microgram quantities. The monoclonal antibodies that were produced from the cell culture were further purified and used in an affinity column for Factor VIII. In using these monoclonal antibodies, they are purified and attached covalently to resins.

The problem came about here, but what are we to do with the Factor VIII that would be manufactured with such implicated material? There was a decision-making process that involved risk assessment by manufacturers and independently by the CDC, the NIH and the FDA. The results of our analysis were that the risk was extremely low, that the purification processing of these antibodies and their subsequent use would not significantly raise the chance of CJD infection above that already present and undetected in these products.

This policy or this decision was made with the involvement and the knowledge of consumer organizations who were notified about the decision-making process and the outcome.

Thank you.

DR. BROWN: Thank you very much, Dr. Weinstein. Do I assume that the length of your speech has obliterated the contribution by Dr. Dubinsky? If so, I would suggest that the remaining speakers this morning take a very hard look at what they are saying and get to the core of what they are saying expeditiously because we will not have overruns on presentations. Dr. Dubinsky?

P. Michael Dubinsky

MR. DUBINSKY: Thank you.

(Slide)

My task this morning for the Committee is to very briefly outline for your information the Agency's definition related to some of the terms that you have been hearing this morning: market withdrawal; you have heard the term recall used. We wanted to be sure that these terms and what they mean to FDA and to the regulated industry are clear. These definitions are taken from the Code of Federal Regulations, where they are published in Part VII of Title 21.

First, a recall is a firm's removal or correction of a marketed product that FDA considers to be in violation of the laws it administers, and against which the Agency would seek a legal action, for example, a seizure action of products, if a firm did not take a step themselves to either

remove a product from use channels or to perhaps make a correction in labeling. We call that a field correction. Recalls are generally voluntary. Firms almost universally take the voluntary step of acting to correct a violative product in use channels.

(Slide)

You have heard the term market withdrawal used extensively this morning. A market withdrawal is a firm's removal or correction of a distributed product which involves a minor violation that would not be subject to legal action by FDA or which involves no violation. The actions that have been taken by the plasma derivative manufacturers and, for that matter, some blood establishments related to the products associated with the CJD issues have been considered market withdrawals by the Food and Drug Administration.

(Slide)

The last definition I wanted to mention, although it hasn't been used, is an official one. It is called stock recovery. This may have occurred in some situations regarding these products, that is, a firm's removal or correction of a product that has not been marketed or that has not left their direct control. The product is located on the premises owned by or under the control of the firm

and no portion of the lot has been released for sale or use.

The FDA, by program, does not follow up on market withdrawals in the same oversight fashion that we do for recalls, for the most part, because it does not involve either a violative product or one for which the violation is so nominal that we would not take an action. However, we have done some things with regard to these product removals that have been made for plasma derivatives.

For example, we would not normally publicize market withdrawals. FDA has publicized the market withdrawal steps by derivative manufacturers on our Worldwide Web Site. We have listed the lot numbers of products, for instance, that have been withdrawn.

Secondly, we have taken steps during inspectional reviews to do two things. One, to review a firm's procedures for both recalls and market withdrawals to determine if they are satisfactory in our opinion, and we have taken steps to identify what they have done with quarantined or returned products. We have also taken steps to review the letters that manufacturers issue to consignees who have received these products that they are withdrawing from use channels.

The information we have suggests that firms have been destroying the implicated products that they do receive

back. Some may be holding portions in quarantine, however.

This information provides you with a brief overview of the terms we use and what they mean to us in Food and Drug and to the industry we regulate. Thank you.

DR. BROWN: Thank you very much. We continue with FDA presentations. This will be by Dr. Ruth Wolff, Office of Therapeutics Research and Review.

FDA-Regulated Products Manufactured with or Containing Blood Components or Plasma Derivatives

Ruth H. Wolff, Ph.D.

DR. WOLFF: Thank you, Mr. Chairman.

(Slide)

Plasma derivatives, most often transferrin or albumin, may be utilized in all stages of manufacture of biological products from the initial stages in cell culture through the generation of the cell banks and production cells, fermentation, purification, up to and including formulation, thereby affecting products as diverse as cellular and gene therapies, monoclonal antibodies and recombinant proteins. These biological products may be administered directly or may be used in the manufacture of yet other biological products.

(Slide)

For example, monoclonal antibodies may be used in the purification of other biological products, such as the use of affinity columns for specific proteins or selection of specific cell populations from heterogeneous populations of precursors to affect antibody-based cell sorting or antibody-based purging. Or, recombinant proteins and monoclonal antibodies may be added to culture media to generate specific cell subpopulations from heterogeneous populations of precursors to affect cell activation or growth promotion. Selection may be positive or negative and, in some cases, low levels of the selective agent may be administered to the patient.

Procedures such as these described may also be used in tandem. For example, cell populations generated using monoclonal antibody selection may be administered directly to patients or may be further selected through the use of additional monoclonal antibodies and/or recombinant proteins.

(Slide)

The manufacturing community, acutely aware of these issues, has been working for some time to remove plasma derivatives from their manufacturing processes. Alternatives to transferrin for tissue culture have been and continue to be explored. However, employing an alternative

is not always straightforward. Changes in culture medium components can and have led to changes in cell culture parameters which, in turn, can and have led to changes in biological products themselves. These changes need to be evaluated to determine whether the resulting product is comparable to the original. If the answer is yes, minimal additional data will be needed for the alternative medium component to be considered acceptable. If, however, the resulting product does not bear the same profile the impact would be extensive.

Similarly, alternative excipients are under study. As with culture medium changes, an evaluation of the impact of the proposed excipient on the biological product, in addition to an assessment of the stability of the product in the new presentation, is needed.

It should be kept in mind that there may be cases for which no replacement is possible. Therefore, a paradigm for evaluation of these products is needed. Thank you.

DR. BROWN: Thank you, Dr. Wolff. Dr. Richman, from the Office of Vaccines Research and Review in the FDA.

Paul Richman, Ph.D.

DR. RICHMAN: Thank you. In this short presentation I would like to go through the plasma derivatives used in products regulated by CBER's Office of

Vaccines, and the impact that the issues under discussion today may have on these products.

(Slide)

On the first overhead I have listed the licensed products regulated by the Office of Vaccines that contain or use in processing products derived from human plasma. Allergenic extracts are used for the diagnosis and treatment of allergy and many of these contain HSA either directly formulated into the product as a stabilizer, or HSA as a component of the diluent recommended for use with this products by the manufacturer. We have a skin test antigen for cellular hypersensitivity testing which contains HSA as a stabilizer. There are two different viral vaccines that we regulate that contain HSA either used in processing or added as a stabilizer. Finally, there is one therapeutic product that contains HSA as a stabilizer.

(Slide)

The issues being discussed today may impact on the following possible scenarios regarding these products: A product shortage situation, for example, the withdrawal of a product because the HSA is withdrawn could result in a shortage of a needed vaccine. At least one of the viral vaccines is a sole-source product, and the bacterial toxin used therapeutically is also a sole-source product. It is a

realistic scenario that we may be faced with a product shortage situation from a market withdrawal of a sole-source product.

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Allergenic products are routinely formulated into prescription sets that are used by individual patients. The same vial of product may be used for six months to a year. If the HSA that was formulated into such a product is withdrawn, the withdrawal prescription set would impact on the patient in the following ways: A new prescription set would need to be formulated and the patient may need to be reevaluated, thereby disrupting therapy for the patient. The reason for the withdrawal would need to be explained to the patient. This may be the cause of anxiety on the part of the patient for what is being considered a low level risk.

Discussion of these issues are part of the charge to the Committee today. I would like to mention that transferrin is also used in cell culture for experimental products regulated by the Office of Vaccines and, indeed, by most of the branches of CBER. TSE issues associated with this product would, therefore, impact on our experimental products as well. Thank you.

DR. BROWN: Thank you very much. We now have two

presentations from the industry. The first will be given by Michael Fournel, who is the Vice President of the Research and Technology Section from the Bayer Corporation.

Manufacture of FDA-Regulated Products Using Human Plasma Derivatives

MR. FOURNEL: Thank you, Dr. Brown. In addition to my affiliation with the Bayer Corporation, I am appearing today as a representative of Pharma, and it is in that capacity that I am primarily speaking.

What I would like to do is give you and overview of some of the manufacturing issues associated with the generation of plasma derivatives and biotechnology products, and how studies that have been done and are currently under way may provide some guidance with respect to the overall risk with these products.

(Slide)

As you are aware, many biotech products are probably not affected by the discussion that we are having today as many of them do not have any plasma-derived components associated with them. However, for those that are potentially exposed, I would remind you of the many comments that have already been made, that is, the risks are still somewhat hypothetical. The infectious agent has not been identified or quantitated in human blood or blood

components. No evidence for transmission of CJD by transfusion even in high risk groups, including those who have received cryoprecipitate, has been reported so far in a conclusive fashion. Epidemiology studies, surveillance programs and look-back efforts till today have found no evidence for transmission.

The point I would like to address in the rest of my talk, however, is the fact that the processes for the manufacture of both plasma derivatives and biotechnology products have the capacity for the clearance of infectivity.

(Slide)

In this presentation, I have made several assumptions for the discussion. These are somewhat controversial to some degree, and I don't know if we will get into this discussion but let me just say for the modeling that I am going to show you, these are the assumptions that I have made.

The first is that the agents responsible for infectivity are potentially present in human plasma. I think the studies from Drs. Brown and Rohwer most recently and others in the literature certainly raise that possibility. They may be present in human plasma obtained from subclinically infected individuals at levels, let's say, less than 100 infectious units/ml. Most of the results

I have seen are somewhat lower than this number so for the sake of this argument I have used 100 as the number.

The second, and perhaps more controversial issue, is the question of whether rodent scrapie is a relevant model for TSE infectivity potentially present in human plasma. There are several lines of evidence to suggest this, for example, the fact that the Pr-P sequence homologies and biochemical equivalence between species have been well established in the literature, and there is a historical data base associated with the use of this rodent scrapie to model TSE.

We believe, and I think there is general agreement, that the Pr-PRES associated with infectivity is required but may not be necessarily responsible for infection in animal models. We could probably spend all day discussing that subject.

Most of the experiments that have been done, and the ones that I will talk to you about today, have used whole brain homogenates from rodents as the carrier or as the source of infectious material, and the question of the relationship of this homogenate-derived infectivity to blood-borne infectivity can be an additional subject for discussion.

The final point I would make is that process

clearance studies that are done with rodent scrapie are relevant for all TSE agents potentially present in human plasma.

So this is a general outline of the assumptions that are used in the following slides.

(Slide)

This somewhat overwhelming slide is an example of the manufacturing complexity that my company, Bayer, is involved with in the fractionation of human plasma into a number of therapeutic products, are shown on the bottom of this slide.

What I would like you to observe on this slide is primarily the green boxes which describe the pathway, if you will, or fractionation from plasma pooling, that is, the pooling of individual units of plasma, to the generation, in particular, of HSA, PPF which you saw mentioned, and also transferrin which actually comes out in this part of the fractionation scheme. So these are the products that are primarily involved in the biotech discussion that is the charge for today's meeting, although there are obviously other plasma products and, again, we could spend a lot of time talking about those.

The point I wanted to make in this slide is to show you these white boxes, and they represent individual

steps in the cascade in the generation of HSA, PPF and transferrin. Each of these represents a separation step which we would call a precipitation, that is, a fractionation of proteins into an insoluble form based on things such as pH, temperature and alcohol. Each of these precipitation steps, as I will show you in a minute, we believe has the capacity to significantly reduce or clear the TSE agent. Dr. Brown has actually shown some data, I believe, previously with respect to the potential for separation, for example, into cryoprecipitate and we would argue that this is a model for all of these other steps as well.

(Slide)

Using data that we, in the Bayer Corporation, have as well as information that was kindly provided to me by Drs. Robert Rohwer and Alan Darling of MA Bioservices, I have attempted on this slide to compile what information we have available to us right now in a generic fashion with respect to process steps' ability to clear the TSE agent. These are studies that were conducted under a variety of conditions, which I am not privy to, supporting a number of different of private concerns that have contracted with these individuals to perform these clearance studies, and I have just provided the generic data which I have tried to

summarize in a readable format on this slide.

So what I have shown here are three different methodologies in the production of plasma proteins or, more importantly, biotech products, and they are chromatography, filtration and what I have labeled as precipitation or extraction. What I have shown on the scale here is the log to the base 10 clearance, that is, how many logs of infectivity are cleared as a result of that individual process step. This has been measured by using infectivity assays in rodents, hamsters or mice, under standard protocols.

What I would like you to notice from this slide -- I am sorry, the print is somewhat small; I tried my best to make it visible -- is that a wide variety of chromatography methodologies have been examined and each of these methodologies, with one notable exception that I can't explain because, again, I don't have the data, represent rather significant potential for clearance of the TSE agent. At least three orders of magnitude or greater has been observed in 10 different experiments that have been conducted. Each of these are independent experiments, with different starting materials, different products. I don't know the specific details beyond that.

Filtration steps have also shown significant

ability to clear and, importantly, nanofiltration and ultrafiltration which represent technologies that have the capacity to provide quite a small pore size for clearance demonstrate very substantial levels of clearance.

Finally, precipitation and extraction steps, such as those I showed you on a previous slide, have also shown very significant abilities to clear the infectivity in these different model systems.

I have not shown on this slide some other methods that have been used. For example, sodium hydroxide treatment is very effective in removing or killing infectivity. But these are all methodologies that involve selective partitioning or clearance, if you will. They are not inactivation methods. These are probably not inactivation methods, I should say; they are primarily clearance methodologies.

(Slide)

So we have discussed two different scenarios thus far. The first one is assuming that the use of a plasma derivative as a therapeutic or as an excipient in a biotechnology product, as the previous speakers have talked about. So under the assumptions that I have told you about before, that plasma has infectious activity of 100 infectious units/ml. It is made into fraction IV or V

derived product and then is most likely used in biotech manufacturing, for example, transferring or HSA.

I have said the fractionation process has at least four potential process clearance steps, these precipitation or centrifugation and filtration steps that I mentioned, and for the sake of the model I assumed that they could clear at least 2 logs of infectivity. Again, as I showed you on the previous slide, that number seems to be quite conservative. And all of the suspect raw materials used as therapy are excipient in the biotech product. That is, there is no reduction because we only used half of a lot.

So based on these 2 logs and 4 steps, this would predict a clearance of at least 8 logs of infectivity that might occur as a result of the generation of the plasma derivative.

(Slide)

Scenario number two is the use of the plasma derivatives as a tissue culture component, that is, in tissue culture fluid in which the cells that produce the biotechnology product are fermented, or as a component -- well, primarily the tissue culture component for the production of the product, or as a component in the processing stream but it really would have to be quite early for this model to apply, as I will relate to at the end.

They are the same assumptions but now I am saying here the biotech purification, assuming that there are 3 different technologies used, which is very common in the production of biotechnology products, have 3 distinct clearance steps, each capable of an additional 3 logs of removal, based again on the data which I showed you in the earlier slide. This would then add to the 8 logs I showed you before, giving an overall safety factor of 17 logs, quite a big number or small number, depending on your point of view.

(Slide)

I have tried to model this in a cartoon fashion or bar-graph fashion on this slide, showing here that in plasma processing, scenario one, we would say that obviously there is no clearance in the pool; that is where the infectivity is residing, and as we go through the various steps of the precipitations, if we add 2 logs by the time we reach Fraction V we have 8 logs of clearance that have occurred. We now put this into TCF so there is no reduction there. Additional 3 logs with each of these 3 types of methodologies that I have mentioned, giving a final product clearance in the range of 17 logs in the second scenario.

(Slide)

In trying to put this into context for this

discussion, we came up with the following model to show you. That is, as many of you are aware, one of the main issues facing the plasma fractionation industry is the potential for viral contamination. The current standard in the world that we are all striving to achieve for enveloped virus clearance -- this really talks about hepatitis C virus as a model -- is that we should have 10 logs of process clearance in our processes. These are regulatory recommendations that exist in the developed world, and ones that we attempt to achieve.

The rationale for this is that a single positive unit of plasma from an HIV-infected or viremic individual that has not yet seroconverted can have as many as 10(7) genome equivalents per milliliter. So if you take that one unit and you dilute it into a plasma pool of 1000 liters, you really have a potential virus load of approximately 4 logs/ml of the pool. So with this level of process clearance one achieves a safety margin of 6 logs. This is a general concept that is accepted in the regulatory environment -- I believe is accepted in the regulatory environment, but certainly it is the target that we shoot for. I am not trying to suggest that the pools, in fact, have this level of infectivity but this is the model that was derived.

Using that model, I have shown here, in the lower part, with respect to expectation for TSE clearance, assuming that we have, again, 100 infectious units/ml from a TSE-positive donor and then 1 infected unit contributes to the pool, we have approximately 1, or actually less than 1, infectious unit/ml in that pool.

If we take the plasma derivative model that I showed you earlier, 8 logs of clearance in fractionation would mean that we would have a safety margin of 8 logs, that is 10(-8) reduction in that infectivity of that 1 unit/ml.

In scenario two, the plasma derivative used in fermentation of a biotech product that safety margin increases by 9 logs due to the clearance that is obtained in the processing, giving us an overall reduction of 17 logs.

The final example, where a human plasma-derived component is used in the processing would affect the total number her. For example, if it were put in the middle of the process stream we might only have 1 or 2 of the processes that I showed contributing to this reduction. But this at least gives you some idea of the range of magnitude that exists, or that we believe exists for clearance of agents from human plasma relative to the current standard that we operate with in the world. We and others are

actively working to validate and verify these numbers using the appropriate model systems.

Thank you.

DR. BROWN: Thank you, Dr. Fournel. The final presentation before what will probably be a truncated break period is Dr. Peter Page, from the Red Cross.

Blood Collection, Processing and Fractionating:

Effects of CJD-Related Recalls on Supply

DR. PAGE: I have removed five slides from what I intended to present in an effort to expedite the occurrence of the break.

(Slide)

Just to review, however, the major factors which precipitate product withdrawal, quarantine or consignee notification have to do with post-donation information of a donor developing CJ, having a family history of CJD, having used human pituitary-derived growth hormone, or having received dura mater.

(Slide)

I am giving a few slides on the background of the nature of volunteer blood collections and paid-for plasma donors in the U.S. The left half of the slide refers to the number of donations and the right half of the slide refers to the number of units donated. Every year Red Cross

collects almost 6 million units of whole blood from volunteer donors. Non-Red Cross, non-profit entities collect approximately another 6 million units of whole blood, both with the primary intention of providing components to transfusion recipients and hospitals.

From those 12 million whole blood donations, about 80% of them, for plasma, is not used for transfusion and is considered recovered plasma which is provided for fractionation into derivatives. So from the 8 million donors of volunteer blood, there are about -- these are rough figures -- 1 million liters of volunteer recovered plasma for fractionation into plasma derivatives.

Plasmapheresis donors, on the other hand, who donate only plasma can donate a greater volume of plasma per donation and may donate much more frequently. So there are 14 million donations in units of plasma from a much smaller number of donors, about 1 million, which create a much larger volume of plasma for fractionation, roughly 8 million.

(Slide)

These figures are for the American Red Cross for fiscal year 1996 just to demonstrate the nature of the donors. About 15% of donations per year are first time donors and 85% from donors who have donated before multiple

times over the years. More than half the blood donors come from community groups; about a quarter are collected in the workplace; about an eighth are collected from students; and Red Cross collects a small amount from the military.

(Slide)

The age profile of volunteer whole blood donors is depicted in this slide and demonstrates that there are a percentage of donors over the age of 60, which is the age in which one might more likely expect CJ to be developing, or developing after a donation within the shelf-life of a plasma derivative. I do not have data, but I believe it is generally felt that paid donors represent a generally younger donor population.

(Slide)

Dr. Weinstein described that there is an FDA requirement for blood collecting agencies to have processes to handle post-donation information that becomes apparent to the donor, or he remembers after the donation, or that a family member may call back the Red Cross or the blood collection agency, such as was demonstrated earlier today when a family member has developed CJ and has previously been a blood donor. The American Red Cross, which collects half the whole blood in the U.S., has 200 to 300 or so reports per month -- this is 1996 and early 1997 -- of that

nature.

(Slide)

Only a very small number of those post-donation reports, as demonstrated by red at the top of these columns, relate to cases of CJ. Many of the others, each of which is investigated, reflect information the donor provides which may have no pertinence to the safety of the product.

(Slide)

The four columns on the right reflect a donor developing Creutzfeldt-Jakob, a donor telling us later that he may have received human pituitary-derived growth hormone, GH, that he may have received a dura mater, DM, transplant, or that he now knows that he has more than one blood relative with CJD.

This goes back to August, 1995, and shows the number of initial reports of each of these four categories that we have received. The next line is those reports refuted by documentation. As it turns out, all 14 of the original verbal reports of CJ were confirmed by autopsy and neurologist diagnosis or other clinical information corroborating the great likelihood of the person really having CJ.

However, for persons telling us that they have growth hormone, about half are refuted by documentation,

which I will give examples of on the next slide. Some of those who report to us that they think they may have gotten a dura mater, when hospital records are obtained it is clear that they did not receive a dura mater transplant at all. There were several reports of people thinking they had more than one family member with CJ, but when documentation of the autopsy or other results from the family members were obtained, they showed that they did not have CJ.

The number of plasma units involved in the reports in these four categories is given on the last line and reflects the fact that a given report from a given donor may reflect multiple donations, which could be in different pools, in different lots of each of the plasma derivatives.

(Slide)

As I mentioned, many of the donors who come back and say "my mother now tells me when I was a child I got a shot of what I think was growth hormone," in those examples where we have been able to get records, which is not all of them, in fact, they received testosterone steroids, chorionic gonadotropin or other injections which were not a basis for product withdrawal. In some of those instances products were on hold for a period of time while we went back to the ancient records to try and determine this information.

(Slide)

The number of withdrawals that we have had as of earlier last month for each of the four categories showed that we have had 10 withdrawals for CJ, 6 related to growth hormone receipt, 2 to dura mater transplant, and 2 related to family history. Some cases of reports that were confirmed do not result in withdrawal because prior whole blood donations may not have resulted in the plasma being fractionated. The plasma could have been used for single-donor transfusion, outdated or lost for other reasons. Also, some of the earlier donations may have been so long ago that there are no in-dated or potentially in-dated products remaining.

(Slide)

The United States policy on CJ's effect on Red Cross derivatives in 6 months of this year, from April through September of 1997, are demonstrated here. We have had 6 episodes of withdrawal. Some withdrawal notifications of lot numbers included a couple of donors at a time. But it shows that there has been a relatively even distribution. There have been 6 withdrawals, 3 were in July and 3 were in September, and they have involved a variety of CJ, growth hormone and dura mater but no family history recently. The number of lots withdrawn in equivalent units of albumin,

grams of intravenous gamma globulin and international units of anti-hemophilic factor are listed, totalling in the 6-month period 70 lots of albumin, 20 lots of gamma globulin, and 6 lots of AHF.

(Slide)

As to the amount of final product itself, the first line shows the total amount of product withdrawn by Red Cross or quarantined and destroyed, or in-process and not further processed up through April of 1997, showing almost 50,000 equivalent units of albumin, over 100,000 grams of gamma globulin and almost 100 million units of AHF. In the subsequent 6 months of this year, which is a half year, the numbers show over 9000 equivalent units of albumin, 13,000 grams of gamma globulin and almost 300 million units of AHF. Currently on hold pending further investigation of diagnosis or medical history, we have some additional product on hold right now. So the totals show 80,000 equivalent units of albumin, almost 200,000 gams of gamma globulin and over 100 million units of AHF. An average hemophiliac may receive between 50,000 and 10,000 units per year in developed countries. So that amount of AHF alone would be enough to treat 100 to 200 hemophiliac patients for 10 years.

Currently, the American Red Cross has back orders

for albumin of over 100,000 equivalent units and back orders for gamma globulin of over 80,000 grams. So we do not have product to meet those orders that we have had from our customers.

(Slide)

We did a survey of 140 of our primarily hospital customers earlier this year, and found that customers, hospital pharmacies for example, on the average maintain only 2-3 days use worth of albumin and maybe 10-14 days of intravenous gamma globulin, and anti-hemophilic factor is variable depending upon the institution. Some, however, order it for just in time use.

(Slide)

As I mentioned, we have and have had back orders for hospitals and home care companies. There have been other recalls and quarantines in the business which have compounded the effect on adequacy of supply, and our customers' number one complaint to us is lack of product or lack of reliability of availability of product.

(Slide)

It was suggested that I mention the financial effect that the U.S. policy on CJ withdrawals have had on the American Red Cross. That is only one half of the volunteer blood industry. Up through April of 1997, there

has been just over $106 million that we have not received in revenue as a result of this policy. This does not include product withdrawn that was not returned. This includes product in process, inventory under our control and products returned. In the 6 months, April to September of 1997, that figure is over $13 million for us, not counting over $2 million on hold pending further investigation on our part. So the total for us so far is well over $120 million. The 6-month total for us is at least $13 million. So annually one would expect about a $26 million negative financial effect on the American Red Cross.

I have been told by members of IPPIA that in calendar year 1997, year to date for the first 9 months, that there has been a negative $30 million financial effect upon their industry for recalls of this nature.

Thank you.

DR. BROWN: Thank you very much, Dr. Page. It is now 10:40 and I think we will have a break and return here at 11:00 to three presentations, the last three presentations before the lunch break and our Committee questions. All three presentations will have to do with surveillance and/or experimental data. So, again, at eleven o'clock we begin again.

(Brief recess)

DR. BROWN: We are going to hear first a presentation by Dr. Robert Rohwer, who is associated with the University of Maryland and the VA Medical center, and who worked in our laboratory at the National Institutes of Health for several years before his present position. He will present what today will be the unique exposition of actual experimental data that may bear on the problems that we are discussing. Dr. Rohwer?

Potential Infectivity of Blood from Subjects with TSE and Effects of Fractionating on Infectivity: Experimental Studies

DR. ROHWER: Yes, thank you. Unfortunately, one of the reasons that we are so burdened in our deliberations about what to do about the CJD exposure of blood is that there is so little data in the literature on this problem and the role of blood and blood-borne infectivity in these diseases. Following the media attention that was given the withdrawal in 1994, Paul Brown and I together and independently embarked on looking into this by putting on a number of experiments. That work is ongoing. These experiments take quite a while to develop to a presentable form, and what I am going to show you today is the results of three lines of investigation which have matured to the

point where they can be presented, and we do not expect any deviation from the results that I present here today and the final experiment.

(Slide)

So we will begin by talking about some blood fractionation experiments of two types, one in which we spiked human blood with hamster infectivity and then carried it through the blood separation and plasma fractionation process and tracked where the infectivity went in the various components and fractions.

In the second fractionation experiment we used blood itself, blood that was intrinsically infected by virtue of the infection borne by a CJD-adapted mouse strain in the mouse. We took the mouse blood itself and fractionated it.

Then I will talk some more about some other experiments in which the hamster model of scrapie was used and the blood from infected hamsters was transfused into other hamsters to see whether the infection could be transmitted by this route, and the titer of this blood was measured directly by inoculation into hamsters, and we looked at the effect of inoculation route and dose on titer.

(Slide)

We are going to start with fractionation

experiments. In thinking about this type of experiment, it is a little bit hard to know how to go about it. The problem is that we don't expect there to be very much infectivity in the blood. This is one of the reasons why it is a neglected subject. It is very hard to work with. There is nothing there particularly. So if we do start with blood and work only with blood we can expect very low titers, long incubation times as a consequence of that, and the sensitivity of the final result will be low. On the other hand, the context will be exactly right. This is the way the infectivity is in blood and the fractionation should be fairly accurate.

If we spike, we have the advantage that we can start with a very high titer because we will use brain-derived material where the titers are very high. The incubation time will be short; sensitivity high. But the relevance is unknown. We don't know whether we are just simply looking at the way in which brain homogenate in this case fractionates by these same procedures.

(Slide)

This is a diagram laying out how the experiment was done. In this particular instance, we took a sick hamster, dying of hamster-adapted scrapie, took the brain, trypsinized it, dispersed it into a cellular fraction --

these were live cells -- mixed it with a unit of human blood and then carried out a fractionation that is analogous to the blood-bag fractionation that is carried out on whole blood units from humans. This was human blood. We then took the plasma fraction of that and further fractionated it into cryoprecipitate I, II, III, IV and V. Each one of these components and fractions was then serially diluted 8 times. These are 10-fold serial dilutions. Each dilution was inoculated intracerebrally into 4 recipient hamsters, or a cage full of hamsters. These animals were then put on the shelf and watched until they came down with the disease.

We get an idea of what the redistribution of the infectivity is by the final titer in these animals, which is indicated by which dilutions kill. The first few might kill. Then you start getting dilutions that don't kill. So you know the titer falls right in here somewhere.

(Slide)

This overhead summarizes the results of this hamster spiking experiment. Basically, the major components all had essentially the same titer -- the spiked, the whole blood, white blood cells, red blood cells. We didn't see any differences here within the sensitivity of this assay, which is only about a half log to a log of fluctuation.

There may have been less material in the plasma

but this is actually within the range of the sensitivity of the assay or precision of the assay as well, so I wouldn't make a great deal about this.

(Slide)

On the other hand, if we look at plasma itself and the plasma fractionation, we had some dramatic changes. This is the infectivity relative to plasma. So normalizing everything to the amount of infectivity that was recovered in plasma, we got vast reductions in going from plasma to cryo, I plus II, plus III, IV and V, and these are actually the fractions recovered, here.

The point I want to make is that such infectivity as we did recover from plasma was mostly in this cryo fraction and in I plus II plus III, and you will see when we look at blood itself, taken from a CJD-infected mouse, that we got the same picture, here. Recovery from albumin was extremely low, 0.00008.

(Slide)

Now let's talk about the CJD experiment. In this case, because you can't take very much blood from a single mouse, a cohort of mice were inoculated with mouse-adapted Creutzfeldt-Jakob disease. They were allowed to incubate the disease until they became clinically ill, and when most of these animals were showing clinical illness all of them

were killed and their blood was removed by cardiac puncture at that point and pooled so that we had a pool of several hundred milliliters of blood.

This blood was not spiked. We were just using the blood from the mouse itself and any infectivity associated with this blood presumably came from the infection. This was carried through the exact same fractionation scheme as before, except this time instead of doing serial dilutions, since we didn't expect much infectivity in the blood anyway, we simply inoculated as much of it as possible from each one of these fractions into large groups of mice and then incubated those mice for a year, and looked to see how many mice contracted the disease out of inoculated.

This is a summary of the results, down here on the bottom. So, for example, we inoculated 145 mice with plasma and 13 of those eventually contracted the disease. That is actually out of date because it is actually 16.

(Slide)

This is the same data tabulated. I present this table just to show you that there were technical problems in doing this experiment and those should be taken into consideration when considering the final result. Basically, we found that many of these components could not be inoculated directly. We had to dilute them first. So the

representation of the original volume was not as great as we had hoped. Nevertheless, when all was said and done, at least for the plasma fractions we were able to inoculate a significant proportion of the material that was made. So, for example, here, for cryoprecipitate we inoculated, all told, 27% of the total cryo prepared by this procedure. In the case of albumin, 28%.

Over here is animals inoculated versus animals that were ultimately positive. You can see that among the components 2/12 animals from the white blood cell fraction contracted the disease, but that was after inoculating only 2% of the white blood cell fraction. If we correct that to the total amount of white blood cells that were collected, the volume collected, we would have had a representation in the entire sample of about 48 animals positive.

A big surprise for us, because we had expected all of the infectivity to be in the white blood cell fraction from prior work, and just also for theoretical reasons -- this material is cell associated, and a big surprise for us was that a very large fraction of the infectivity appeared to be associated with plasma itself.

If we take this total infectivity -- add these up -- the total recovered infectivity is 427, by the total 45 ml blood assayed, we get a titer for blood of about 10

infectious units/ml. As you will see shortly, this is consistent with what we found in the hamster model as well.

Very consistent with the spiking experiment, what infectivity we found in the plasma fractions was in the cryo and in I plus II plus III. This is exactly what you would find for non-envelope viruses as well in these same types of fractionations. There was, however, a big overall reduction in total infectivity recovered from plasma fractions compared to the infectivity in whole blood.

(Slide)

What can we learn from this? One, that the blood titers are low; that both buffy coat and plasma bear infectivity; that the infectivity was recovered in plasma fractions; and I think most importantly, that in spite of the low titer in these animal models blood can still be used profitably as an experimental material and we can work directly with blood using these types of approaches.

(Slide)

In the spiking experiment I think it is important to note that for all the caveats that are associated with that, the distribution that we saw in the spiking experiment was consistent with the CJD experiment, and that processing resulted in significant removals of infectivity.

(Slide)

I am going to talk about another series of experiments which involved again animal blood. In this case, we are using a hamster model and this is hamster-adapted scrapie. The hamsters were inoculated with scrapie. When they got sick they were bled. They were killed. The blood was removed by cardiac puncture, and from a given hamster we can get between 3-5 ml of blood. This blood was used in all of these experiments in the following way: 2 ml of the blood was transfused directly into another recipient hamster; 2 ml of the blood, when we had enough blood, was used to prepare white blood cells. We had hoped that this would be a way of concentrating the infectivity in the blood for assaying whether there was actually any infectivity there in the first place. We didn't know when we started these experiments whether the hamster model, especially by the ic route, would give us blood infectivity. So this was a way of concentrating it, 2 ml of blood into 50 mcl so we only had to inoculate 1 animal to see whether there was infectivity in the blood.

As you will see, this didn't work as expected. Just to make sure we weren't missing something, in several instances where we had sufficient blood we too a whole milliliter of blood and inoculated it without any fractionation, any assumptions at all, into 20 hamsters. It

takes 20 hamsters to inoculate a milliliter of blood because you can only inoculate 50 microliters at a time into the head of a hamster, which is the most sensitive way of looking for infectivity in anything.

(Slide)

We also did three types of experiments. We inoculated some animals with a very high dose of inoculum by ic. This is the way all experimental work to date has been done in the past. We were concerned that, because the incubation time is short, what we might be isolating in the blood of these animals would be the inoculum itself. To test this, we also did a group of animals at a limiting dilution of inoculum where we only inoculated maybe 1-10 infectious doses/ml. Any infectivity which subsequently showed up in the blood of these animals would have to have been derived from the infection itself; it could not have come from the inoculum. We also explored the ip route, both in clinical disease and preclinical disease simply because we knew that others had seen infectivity by that route.

(Slide)

Here are the results. These two tables that I am going to show you here are organized in the following way: Each line is the results of the downstream subsequent infections with the blood taken from a single hamster. So,

for example, the blood from this hamster was transfused and 630 days after transfusion we still have no infection in that animal. We did not inoculate any whole blood. In this case, we transfused the blood from this hamster, which had received a high dose ic inoculation, and after 261 days this animal came down with scrapie. The transfusion recipient came down with scrapie.

When we inoculated the whole blood from this animal, 50 mcl at a time into 20 animals, 11 of those animals are now sick with scrapie. So we can say in this case that this blood contained scrapie and when this blood was transfused into a naive animal it caused an infection.

Here is another transfusion which did not cause an infection. Here are some low dose ic donors. These are animals inoculated with limiting dilution. We saw no transfusion transmissions from these animals, but the blood itself was infectious and 2/20 animals inoculated have now come down with disease.

(Slide)

Next I am going to talk about these ip inoculations.

(Slide)

In this case, the animals were inoculated by the ip route with a high dose. One group was bred during

preclinical disease and another during clinical disease. None of the transfusions from either of these groups have transmitted the disease. We had enough blood from a number of these animals to do buffy coat inoculations and, very surprising to me, only one of these buffy coats or white blood cell fractions transmitted.

On the other hand, in every instance where we had blood for whole blood inoculations every one of these bloods has proven to harbor infectivity. Here is a case where we only had enough blood to inoculate 8 animals, which is why this is truncated at this point, right here. Extrapolated out to 20 animals, we would expect about 2 units of infectivity for this animal, 5, 5, 12 and 7. So, again, the titer in the blood by these experiments is about 2-10 infectious units/ml.

(Slide)

What can we take home from this? Well, there are 1-12 infectious units/ml of infectivity in blood in this model. The infectivity is not exclusively in the buffy coat because we had several instances in which we inoculated both whole blood in buffy coat and the buffy coats did not come down even though the whole blood had 5-10 infectious units/ml. We should have been putting, if it had all been in the buffy coat, 10-20 infectious units into the animal

via the buffy coat. This suggests again, consistent with the CJD mouse experiment, that there is infectivity in other components besides the cellular component.

Only one transmission occurred out of 22 transfusions done. We have another 100 transfusions under way, which I hope will give us some sort of statistic because right now we don't know whether this represents 1 in 22 transfusions would do or 1 in 22 million. There is no statistic that we can attach to this number. Was this a fluke or is it something that would happen regularly if we had a large enough cohort?

The other caveat that I have to point out is that the only transfusion that worked was a transfusion that came from an animal where the donor animal itself had received a higher titer of inoculum to cause the infection. Were we re-isolating the inoculum, and is the inoculum in some different form than the infectivity that is derived from the infection itself? We don't know that yet but we are doing experiments to answer that.

Finally, blood infectivity was present during preclinical disease and a limiting dose inoculation resulted in blood infectivity. This is extremely important because it removes this lingering doubt about whether this experimental work that has been done to date is relevant or

not. This infectivity could only have come from the infection itself, not from the inoculum.

(Slide)

The final slide -- how robust are these results? I want to remind you that even though it is very comforting that all three of these experiments have provided consistent results, nevertheless, they are just three experiments, and we have explored only two routes of inoculation, ic and ip. We have looked at dose and incubation time. We have now looked at two doses, high dose and low dose. They both seem to cause blood-borne infectivity. But incubation time could be a very important feature. These are relatively short incubation time models and what happens in a longer incubation time model -- most people don't like to work with those types of models, but it could be a relevant parameter in this story.

We have looked at a total of two host strain combinations here. Many more should be investigated, especially the BSE models. The fractionation parameters that were used here were generic fractionations. We have no idea how robust these protocols are with respect to the subtle variations that occur between manufacturing protocols, for example, and how that would affect the final result.

Finally, it is hard to assign any statistical significance to such a limited data set, but that can be remedied with more experiments and those experiments are under way.

Thank you.

DR. BROWN: Thank you very much Dr. Rohwer. We now go from the laboratory to the field with three discussions about epidemiology of CJD with respect to blood and blood components, first from Dr. Marian Sullivan, from the National Blood Data Resource Center in Bethesda.

Epidemiological Studies of CJD and Blood, Blood Components and Derivatives

DR. SULLIVAN: Good morning.

(Slide)

The CJD investigational look-back study is now in its third study year. This past August, the responsibility for the long-term conduct of the study was transferred from the American Red Cross, where it was initiated, to the National Blood Data Resource Center, a non-profit, independent data center recently founded by the American Association of Blood Banks.

In the next few minutes I would like to quickly review the fundamentals of the study for you, which I initially presented to this Committee last year, and provide

you with an update of the results to this point.

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The Red Cross remains the largest contributor of the data to the look-back study, providing information on donor cases and transfusion recipients. Other collaborators in this study are the CDC and the New York Blood Center.

The study began late in 1994, when the FDA Office of Blood Research and Review called for an assessment of the risk of CJD transmission to recipients of donated blood and blood products. This was triggered by information that a frequent Red Cross blood donor had been diagnosed with CJD.

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The look-back study which resulted is designed to collect outcome data for recipients of blood components from prior donations from donors who are subsequently diagnosed with CJD. It is important to note that donors who were determined merely to be at increased risk for CJD are not included in this study. Look-back of newly identified donor cases is initiated on a continuing basis. The protocol calls for a disposition record search for single donor components for all donations from a donor with CJD. Consignee notification, identification of recipients and occasionally vital status information is volunteered at this point by the transfusion service or the physician. An

annual search of the National Death Index Plus, which is a relatively new nationwide data base available through the National Centers for Health Statistics, which provides multiple cause of death data which are reviewed for CJD or any suspicious neurological conditions. As a final point, I would like to emphasize that no recipient notification occurs in the context of this study.

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Look-back data have been received thus far for 14 donor CJD cases which occurred between 1975 and 1996. Two additional cases, which have come to light in 1997, are currently under investigation and are not reported here.

Of the 14 completed cases, 10 were laboratory confirmed CJD and 4 were classified as probable based on at least one neurologist's review. Associated with these 14 donor cases were a total of 281 donations which resulted in components released for transfusion. The donations occurred from 1959 to 1996. The median number of donations per CJD case is 8.5, with a range of 1-76.

I would like to note that the efficacy of the look-back process for the study overall has been approximately 60%. As you would expect, it is higher, about 82%, for components transfused within the last 10 years, and the availability of recipient information for components

released more than 10 years ago is only about 20%. The poor availability of transfusion records after 10-15 years is, unfortunately, the major weakness of the look-back study design when applied to a disease with a potentially long incubation period.

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The 14 donor cases are indicated on this map by year of diagnosis and blood center location. As you can see, 3 blood centers have provided data for multiple cases. A total of 180 recipient reports have been received. Of these, 116 are known to be deceased. The cause of death is known for 115 and none was due to CJD. The deceased group had a total of 104.5 years of post-transfusion survival, with a median of less than 6 months and a range of 0-14 years. These data are consistent with those of other look-back studies and reflect the general experience of relatively high mortality in a selected transfused patient population due to underlying disease.

The 64 recipients alive at last report represent 400.5 years of post-transfusion survival, with a median of 5 years and a range of 0-25. Two individuals have left the United States and will have to be considered lost-to-follow-up. The entire study population has a total of 505 years of post-transfusion survival, with a median

survival of 1 year and a range of 0-25.

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We have defined a subgroup of recipients who are of greatest interest to us at this time because they survived at least 5 years post-transfusion, and 42 subjects meet our definition of long-term survivors. Of these, 37 are alive at last report and 5 are deceased. The median survival of this group is 7 years and the range extends to 25 years. In fact, there is 1 25-year survivor and 2 23-year survivors in this group, and 2 of these individuals who are both healthy and in their 50s received an entire unit of whole blood from the same donor within 5 years of the donor's CJD diagnosis.

Lastly, I am frequently asked how many survivors in our study have met or exceeded the average incubation period for the transmission cases in the human pituitary growth hormone transmissions, which is approximately 15 years, I believe, in terms of international cases. The answer is that we have 5 survivors in our study who have met or exceeded that number.

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Another way to look at the survivors in the study is to examine a subgroup that might have the greatest theoretical risk for acquiring the disease based on the

onset of CJD in the respective donors.

In this table, the 14 donors have been stratified according to the number of months between their last blood donation and the onset of CJD. As you can see in column 2, 5 donors were symptomatic within 1 month of donation. In column 3 there are 9 survivors who received components from these donors. I have included not just the final donations from these 5 donors but any other donations within 12 months of disease onset.

So if you add the 3 additional recipients from line 2 with donor onset between 1-6 months, and the 1 recipient on line 3 with donor onset within 12 months, you see that there are 13 total survivors who received a component donated within 1 year of the onset of disease in the donor.

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The distribution of blood components to all study subjects is shown here. Although the number of recipients in the study is 180, 1 deceased recipient received 3 separate components from the same donor on 2 different donation occasions, which results in the total of 182 components here. Sixty-four percent of the recipients received red cells; 19% platelets; 12% FFP; and less than 5% each received cryoprecipitate or whole blood.

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In conclusion, no cases of CJD have occurred in 179 recipients of blood components from 14 donors who subsequently developed CJD. This represents more than 500 person years of post-transfusion survival. A subgroup of 13 survivors received a component donated less than 1 year prior to onset of disease in the donor.

Long-term follow-up of survivors will allow for more accurate estimate of the risk, if any, of transmission by blood components.

I would like to say in closing that now that the study resides at the independent National Blood Data Resource Center, it is our goal that it will become a truly nationwide effort with the participation of all U.S. blood centers that experience a donor CJD case.

I would also like to mention to the Committee that the Data Center hopes to initiate a long-term outcome study of recipients of intravenous immune globulin very early in 1998.

Thank you.

DR. BROWN: Thank you very much. We will now hear from Mike Souci, from the CDC, again, a presentation of epidemiologic information.

Mike Souci, Ph.D.

DR. SOUCI: Good morning.

(Slide)

The Centers for Disease Control has a number of CJD surveillance activities that we are conducting in the hemophilia community, and I would like to give you a brief overview of those projects and results to date this morning.

The first of these includes a survey and continuous monitoring of the 140 or so federally funded hemophilia treatment centers in the United States for clinical cases of CJD.

The second, we conduct an annual review of data from the National Death Index, beginning in 1979, looking at persons who die with a diagnosis of CJD for the existence of coexisting diagnosis of any form of bleeding disorder.

We have conducted both a retrospective and prospective study of brain tissues obtained through autopsy after death among persons with hemophilia or other bleeding disorders.

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We feel that CJD surveillance in the hemophilia and bleeding disorder community is important for several reasons. First, as you heard this morning, the agent has been shown at least experimentally to be present in blood. The clotting factor used by persons with bleeding disorders

is made from large donor plasma pools, and people with hemophilia and other bleeding disorders have now had exposure to these factor products for 15 to 25 years. Combining that with the observation that approximately 25% of the deaths occurring in this community are noted to have symptoms in the last 6 months of their lives, we are concerned about the possibility of perhaps missing or misdiagnosing causes of death among these individuals, and feel it is important that they be investigated.

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Diagnostic criteria for the clinical diagnosis of CJD in our monitoring in the hemophilia treatment centers consist of probable diagnostic criteria, including a history of rapidly advancing dementia with one or more of those clinical signs and symptoms that you see listed there. There are some potentially characteristic EEG changes that are found certain times and, of course, the spongiform degeneration seen on histopathologic exam at autopsy.

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Definitive diagnosis is made on pathologic exam for the presence of amyloid plaques, the presence of prion protein when subjected to special staining techniques, transmission to animal studies and presence of certain gene mutations seen to be present in CJD cases.

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With regard to the retrospective portion of our studies, we conducted a survey of the hemophilia treatment centers for CJD, and this monitoring is continued and there have been no clinical cases of CJD to this point. Also, during that survey we identified autopsy material that had been attained from decedents with bleeding disorders since 1983. We were able to collect that material and take the residual tissue blocks, prepare standard sections of this material by a strict protocol and submit these sections to a panel of three experts for examination for CJD.

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These efforts resulted in our obtaining specimens from 24 autopsies. And 21 of those patients were HIV positive at the time of death and AIDS was either a primary or a contributory cause of death in most of them. In 15 of those 20 with AIDS, there was CNS involvement diagnosed before death as HIV encephalopathy, AIDS dementia and hepatic encephalopathy, among others. There were no diagnoses of CJD prior to death.

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The mean age at death of these subjects was 42 years. As you can see, the cases were primary afflicted with the more severe forms of bleeding disorders, those

which would have exposed them to more use of factor concentrates and more likelihood of contracting an infectious disease.

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This slide just shows the year at which the autopsy material was obtained. You can see that it was relatively constantly obtained over the 14-year period of time that the autopsies were performed.

(Slide)

Just one mention more about the age distribution, I would just point out that while there were some patients that were in the age that might be expected to produce CJD cases, the majority of people were much younger than you would expect from the normal way CJD presents.

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With respect to the results, there was no histopathologic evidence of CJD seen by the reviewers, except in one case the histopathology was uncertain as read by one of the reviewers. Also, one of the decedents was a known recipient from a CJD donor. So the material from those two subjects was further subjected to staining for the prion protein, which was also found to be negative. There was unanimous agreement by the panel that none of the patients had died with CJD.

(Slide)

With respect to the prospective component of the surveillance, we have also implemented this in these hemophilia treatment centers and have asked treatment center staff to identify deaths with CNS symptoms prior to death, and to have the staff request from family members a brain autopsy at the time of death. They also abstract basic data from the patients' medical records, and the specimens then from the brain autopsy are treated according to a standard protocol and developed into specimens from the three brain areas that are then subjected to pathologic exam for the prion protein using the special staining.

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Since January of 1996 we have been working with 52 hemophilia treatment centers who have volunteered to participate in this project, 16 of which we refer to as active sites. Those sites are larger centers and more likely to have decedents, and we have CDC staff that contact them on a very regular basis. The outcomes of that surveillance over this 21-month period -- there were 57 deaths occurring in these centers, 20 of whom had CNS symptoms prior to death and we were able to recover about a third of those brains affected with CNS symptoms.

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Of the 6 autopsies, all of the patients were HIV positive. AIDS was a primary or a contributory cause of the death in half of them, and all had various levels of CNS involvement, 2 diagnosed with dementia and 2 with hepatic encephalopathy. The mean age of death in the prospective component is quite a bit younger than those in the retrospective, only 33 years. Again, we see that these patients are the more severely affected patients and those with the highest risk.

(Slide)

The age distribution here, you can see, that we have none of these patients in the older age group. They are all younger.

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Results on this study to date are no histopathologic evidence of CJD. All of these specimens have been stained for the prion protein and have been negative by both of the techniques shown there. The unequivocal findings of this portion of the surveillance are that none of the patients had died with CJD.

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In summary then, up until this month our surveys and continuing monitoring of the hemophilia community through the hemophilia treatment centers has revealed no

evidence, no suggestion of clinical CJD. The National Death Index review of close to 4000 people by now, among the people with the diagnosis of CJD at death, none have had any bleeding disorder. The retrospective study of 24 brain autopsies were all negative for CJD, and in the prospective study we have 5 results read as negative for CJD and 1 pending.

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With regard to our future plans for this surveillance, we plan to not only continue the surveillance but to broaden it and expand the surveillance to not only to increase the number of hemophilia treatment centers participating, but also to broaden our request that not only those patients just CNS symptoms but all people with hemophilia and bleeding disorder decedents donate brains for this surveillance. We are increasing our technical support to the staff of these treatment centers to help them to obtain these autopsies. As you might imagine, it is a difficult time; it is a difficult process for people who are not trained. We are providing them with material, staff and education to help them to be able to approach families to get autopsies, and we are providing material for them to give to patients to help explain what the surveillance is about and what the importance is. Finally, we are

heightening our awareness in the hemophilia community through national promotional activities at regional and national meetings.

Thank you.

DR. BROWN: Thank you, Dr. Souci. We now will hear the European experience on the surveillance for CJD in the context of risk from blood transmission from Dr. Robert Will.

Robert G. Will, M.D.

DR. WILL: Good morning.

(Slide)

Just to give you a bit of background, surveillance of Creutzfeldt-Jakob disease has been going on in the United Kingdom, going back to 1980, with data in England and Wales systematically going back to 1970, and in Scotland and Northern Ireland back to 1980. So we have a large amount of data systematically collected on CJD. We believe that there is a high degree of case ascertainment, and since 1993 we have been collaborating with other European countries who are carrying out systematic surveillance using similar methodologies.

Between 1980 and 1984 in England and Wales detailed information was obtained in every suspect case in past medical history, which included a history of previous

blood transfusion or previous blood donation. Similar information has been collected since 1990 in the U.K. and in the collaborating countries in Europe since 1993, which covers a population of about 360 million individuals.

I think in brief I can say that we have no definite case in the United Kingdom of CJD that we believe is related to blood transfusion or the use of blood products. I think my own view is that there is no well documented case of that from anywhere. However, inevitably if you collect information in patients of largely middle age you will identify some individuals who previously had a blood transfusion. The question that arose is whether or not the frequency of previous blood transfusion was higher in cases of CJD in comparison to age-match control cases, in case control methodology, and this was carried out between 1983-84, since 1990 and also in the European study.

Essentially, the results of these studies are all the same. This is a previous publication which showed the individuals with CJD who had previously had a blood transfusion, which at that stage was 15 cases out of 92 between 1980-84, was very similar to the age and sex control group. Similarly, in the prospective study, and this data is still the case.

What we believe this evidence shows is that at

least in the case control methodology there is no increased risk to CJD from having previously received a blood transfusion. I think it is reasonable to conclude from this data -- I think it is the only conclusion you can make, that it is most unlikely that blood transfusion can be a common risk factor for CJD.

You will also note on the right that we identified individuals with CJD who had previously acted as blood donors. That was 15% of cases between 1980-84, 16% since 1990.

We have systematic data on the geographical distribution of cases in the United Kingdom. One of these blood donors from around 1980 had been a gold medalist blood donor who had given over 50 units of blood and he had lived in one particular place and had donated blood in one particular place throughout his life. We have been able to look at the distribution of cases of CJD subsequently and really, overall, there is no good evidence of spacial or temporal string of cases anywhere in the United Kingdom and, in particular, there is no good evidence of an excess of cases in the sites where major blood donors with CJD had lived.

I think there is a very important conclusion from these data as well. You will note that about 1/6

individuals with CJD had previous acted as blood donors, and this is from systematic surveillance. This has been borne out in the surveillance in Europe where a similar proportion in other countries in Europe have previously acted as blood donors and subsequently developed CJD. The implication of this is that if you change from a passive to an active surveillance system the number of blood donors who subsequently develop CJD will be a significant proportion of all incident cases, and this may have major implications regarding withdrawal of blood products.

One way of looking at these individuals who have previously received a blood donation is to look at the clinical features of these cases.

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The reason for doing this is that it became clear some years ago, from papers written by Dr. Brown and others, that in individuals who develop CJD after growth hormone treatment the clinical features in these cases were rather distinct from classical CJD in that the great majority presented with a cerebellar syndrome without very much in the way in the evidence of dementia. This may well be related to the route of inoculation or the agent. This may be a determinant to clinical presentation.

So what was done was to look at those individuals

with CJD who had previously received a blood transfusion to see whether the clinical features in these cases was similar to sporadic CJD or to growth hormone-related CJD. Essentially, the clinical features in cases of CJD in the United Kingdom who had received a blood transfusion is identical to sporadic CJD, providing some additional evidence that these cases are not causally linked to the previous blood transfusion.

(Slide)

This is data from the European study, again showing previous history of blood transfusion in the patients who subsequently developed CJD. We now have very much larger numbers. Again, this data shows no difference in the frequency of blood transfusion in cases and controls.

There are caveats to the interpretation of this data because in all these studies we have used hospital-based controls which does introduce the potential of bias. In the United Kingdom study we have excluded any history of blood transfusion related to the diagnosis of the control case when it was identified. If you look at the European study, what we have done is to stratify these results, look at the relative risk depending upon the timing of the blood transfusion prior to admission to the study. Again, there is no good evidence that blood transfusion is a

risk factor for CJD.

(Slide)

The look-back study I was going to mention -- Dr. Sullivan's study is clearly very much more thorough than the previously described study which was just an isolated study from Germany, which I will not go through the details of but, essentially, they identified a blood donor who had donated quite frequently prior to death and could find no evidence that this had resulted in subsequent CJD in any recipient.

We are currently carrying out a look-back study using all the data we have in the United Kingdom, but no results of this study are yet available.

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I would just like to briefly mention the criteria for exclusion for blood donation because we believe that some of the data we have which is, again, systematic, might be quite helpful. Here is a family tree showing an individual we identified with pathologically confirmed Creutzfeldt-Jakob disease. We subsequently discovered that his brother had died of what was called Huntington's chorea, although subsequent review of the pathology of this case showed that it was Creutzfeldt-Jakob disease. In the preceding generations there was a diagnosis of dementia,

organic dementia, neurosyphilis and Huntington's chorea.

The reason I put this up is to illustrate the difficulty in using a family history of CJD as necessarily excluding the presence of this disease in other family members.

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We have been looking at this quite in detail and, just briefly, of all our cases of CJD that we have identified, 12% of cases are actually genetic with PrPG mutations. Of the genetic cases, 52% are not considered familial, there is no good family history; 22% of actual sporadic cases have a history of dementia, which adds another complication; and 70% overall of the genetic cases had a family history of dementia per se.

What is important in this group is that if you had asked the question, do you have a family history of CJD, a small majority would say, no, there is no family history of CJD or of dementia and, actually, within the group of genetic cases only about 1/3 were aware of a family history of CJD, and in these 1/3 only a very small minority were aware of more than 1 family member affected.

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I would just like to finish with something that may be regarded as slightly irrelevant to this meeting but I

felt I should put it up for the sake of completeness, in the United Kingdom a new type of Creutzfeldt-Jakob disease has been identified, which has been designated nvCJD which is believed to be related causally to contamination with the BSE agent.

This is the biopsy of a tonsil from one of these cases that was obtained at postmortem and shows PrP immunostaining. It was within the tonsilar tissue. We believe that in a number of cases of classical CJD where the tonsil has been looked at, for example, from Japan, there is no such staining in the tonsilar tissue. We believe that this, amongst other things, does raise the possibility, at least a theoretical possibility, that although the risks from blood in classical CJD we regard probably as very small indeed, with really no good evidence of transmission in blood from the epidemiological data, such as it is, there is a theoretical possibility that in nvCJD the relative risks may be different. Thank you.

DR. BROWN: Thank you very much, Dr. Will. It also raises the possibility that nvCJD, if the tonsilar observation holds up, could conceivably be a source of environmental contamination where sporadic CJD is not. That is to say, if the tonsil is infectious possibly the gastrointestinal tract and its contents and saliva could

also come in for some concern. So typically in sporadic CJD we have no evidence for a means by which it could be horizontally transmitted. Possibly the new-variant might present us with an exception.

There is a coda to this morning's presentations, and I am going to give Dr. Rohwer another four to five minutes to conclude this discussion.

Robert G. Rohwer, M.D.

(Slide)

DR. ROHWER: I simply want to enlarge on the remarks of Donald Tankersley earlier, and extend that discussion to the whole concept of withdrawals and share with you my perspective on that.

Just going over his same numerology quickly, the incidence of clinical CJD is 1/million/year worldwide pretty much, which means that among the 240 million people in the United States we should have about 250 cases a year, and that is what we see here. But the prevalence of CJD infection could be much greater than that because the prevalence is the incidence times the incubation time. We have to include all those people who are incubating the disease, i.e., carrying the diseases in the prevalence rate. If the incubation time, for example, were 40 years and we know from the Kuru story and the some of the human growth

hormone cases that it can be this long, we would multiply 1/million times 240 million -- I don't think that arithmetic is correct there, anyway, we would multiply this, the 1/million/year times the incubation time and we would end up with 10,000 carriers. If it was 20 years it would be 5,000, and 10 years it would be 2,500.

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Then how does this figure into the exposure of the blood supply to CJD? Well, 10% of the population donates blood, or that is the number that is frequently cited. That would mean there are 24 million donors. Of those 24 million donors, there should be 25 clinical CJD cases per year. We are only picking up 5 or 6 according to Peter Page's presentation, for example. So where are these other cases?

Furthermore, there could be as many as 1000, 500, 250, something like that, CJD carriers per year to which the blood supply is exposed and we have no hope of picking those people up because we have no way of diagnosing them or identifying them.

So how does this figure with respect to donors? If we had a 40-year incubation period, this equals 1 carrier/24,000 donors; a 20-year incubation period, 1 carrier/48,000 donors, etc.

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Considering that our pool sizes for plasma and plasma derivatives is on the order of 20,000 donors or better, the point I want to make is simply that we really can't differentiate one pool from another on the basis of identified Creutzfeldt-Jakob disease cases. These are sporadic events and we are only looking at the tip of an iceberg. Basically, most of the exposure is from undiagnosed carriers.

If there is any truth to what we have heard today, we have heard today that we are under-diagnosing, there may be far more of these than we expect. Therefore, virtually all pools must be exposed and this differentiation gives a false sense of security. Nevertheless, I think there is reason to feel confident in our blood supply, and that reason comes not from this type of numerology, not from the experimental work which I presented earlier but, rather, from the epidemiology which suggests not necessarily that this does not occur but, if it does occur, it occurs at such a low level that it has not yet ever come to our attention in spite of the major efforts that people are making right now to identify a connection between transfusion or blood-derived products and these materials.

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Finally, I just want to remind people that I think

what is driving our concern about Creutzfeldt-Jakob disease is not Creutzfeldt-Jakob disease, it is AIDS. There are immense differences between these two diseases which must be taken into account in our considerations here. AIDS was a newly emergent disease in the '80s. Everything changed with the emergence of AIDS. It is a high titer blood-borne disease. In comparison, Creutzfeldt-Jakob disease is probably an ancient disease. It has certainly been around for at least 100 years. The titers in blood are very low titer. It is principally a CNS disease. The main advantage that we have with AIDS is that we can effectively screen for it; with CJD we can't.

Nevertheless, the points I want to make are that the blood supply has been exposed to CJD since the very first transfusion was performed half a century ago and nothing has changed since that time. There is a low, unquantifiable and irreducible risk that is probably associated with exposure to CJD through blood and blood products, but that risk, whatever it is, and we are still trying to measure it and discover it but whatever it is, that risk is unchanged by this withdrawal process. We are still being exposed whether we withdraw or not. For that reason, I question the rationale for withdrawals in the first place.

DR. BROWN: Thank you, Dr. Rohwer. I think we have about a half hour now for questions from the Committee to the speakers. I would like this half hour not to be a discussion amongst members of the Committee with each other as take-offs from questions to the speakers. I would like to limit it so that Committee members who have specific questions to any of the speakers this morning have an opportunity to get an answer. I would ask that the people who are asked questions respond at the floor microphone, please. Larry?

DR. SCHONBERGER: I would like to ask this question or Rob Will or others from the U.K. in terms of what is the policy in Europe or in the United Kingdom with regard to this same issue of blood and plasma, and the rationale for it. I understand it is different.

DR. WILL: My understanding is that there is no policy for withdrawal of blood product in the United Kingdom nor, indeed, I believe in the European Union. I think that is a policy decision that was made a few years ago, presumptively, I believe, because this is a theoretical risk with no good evidence that there has actually been a case, although clearly, as everyone has said, there is a possibility of such a thing happening but we don't have any good evidence that it has happened as yet.

DR. SCHONBERGER: Has the emergence of the nvCJD been discussed in light of that policy?

DR. WILL: Yes, the issue of nvCJD has been discussed and it has been heightened by the fact that three of the nvCJD cases have been blood donors. It is an issue that is under active discussion. It is also important to consider carrying out research projects similar to those described by Dr. Rohwer in relation to infectivity in blood, trying to estimate relative titers of infectivity in comparison with classical CJD. But I stress, again, it is a hypothetical risk and the evidence that we have at the moment does indicate that there may be reasons for being concerned about nvCJD but they are hypothetical arguments.

DR. ROOS: I have a question of Bob Rohwer. I guess there was a theme in both the presentations in which it is important to know really about subclinical disease and infectivity of blood. I wonder whether you would comment about that because it importantly impacts with respect to this carrier state, and also with what we think about infectivity. In other words, your guideline at the moment is that there is a small amount of infectivity from your experimental results and whether one could be off, in fact, with respect to that infectivity during the incubation period time significantly.

DR. ROHWER: If I understand your question correctly, you want to know about the infectious state of blood during preclinical disease and whether the titer could be greater or lesser. Well, the fact of the matter is that we know very little about that. To the extent that it has been looked at experimentally in rodent models, it looks like the entire preclinical period is viremic for these diseases, but the titers also appear to be low level. That is based on incubation time measurements, not on direct titration or the type of experiment that I showed you that we did.

Nevertheless, the idea is that there is probably a low level blood-associated infectivity associated with these diseases. But I think what is urgently needed is a great expansion of these types of studies to look at the preclinical case because I think that is the major source of our exposure and it would be nice to have better numbers attached to preclinical disease. My guess is, if you just want a guess, that it is going to look sort of like the way it looks in clinical disease throughout the whole incubation period.

DR. PRUSINER: Bob, there was an overhead, about fourth from the end of your first presentation, where you were comparing in the hamsters -- and maybe you can find it

and put it back up -- whole blood and buffy coats. I was struck by the fact that one of the buffy coats was positive at about 300 days and there was a whole series of others that were negative. Then there were more whole bloods that were positive than buffy coats. Is this the opposite of mice? How do you interpret all this?

DR. ROHWER: No, I don't believe it is. It is exactly consistent with the observation in the CJD mouse experiment as well, where you cannot account for the infectivity in the plasma by cross-contamination from the buffy coat fraction because the volume of that fraction is so much smaller than the plasma fraction. There was actually a lot more infectivity in the plasma than in the buffy coat.

What it suggests to me is that we have been mistaken, and certainly I was mistaken because the reason I did these white blood cell inoculations was as a way to efficiently inspect the blood for the presence of infectivity, and it was a great surprise to me to find that every blood that we have measured has a low level of infectivity associated with it and, yet, only one of the buffy coats showed infectivity. That buffy coat was a blood that was also positive by direct demonstration but it was not an expected result. But it is consistent with the

result in the blood fractionation experiment in the CJD experiment, which makes me wonder whether infectivity does reside in some other form in blood.

DR. PRUSINER: How many buffy coats were negative? How many did you test? Do you remember? You had one that was positive.

DR. ROHWER: I believe there were 8-10 of them that we did, and there was one positive in that group. There were two very clear-cut cases where we had positive blood and negative buffy coat.

DR. BROWN: Other questions?

DR. PRUSINER: Let me just expand on that for one second, Paul. So in the spleen of the hamster, people generally think titers are lower than in the spleen of the mouse. Is that important in this whole process, do you think, in terms of trying to find the best animal model? You are saying that the mouse and the hamster are equivalent, and I don't know that I am totally convinced of that.

DR. ROHWER: No, I am not saying the mouse and the hamster are equivalent. I am saying that the results obtained in mouse and hamster were consistent. There is a big difference there, and I think a point that I have been trying to make and drive home is that because there is some

variation in these models, we know there is, in order to extrapolate the data from rodent experiments to the human experience or the cattle situation, it is important to look at as many different models as possible, looking for areas in which they are consistent because that is the only data that we are going to have enough confidence to extrapolate to the systems where we can't do direct experiments.

DR. BROWN: I don't know if I am right in saying this or not, but to the best of my knowledge the only experimental study in which sequential measurements of infectivity were done in both the spleen and the blood was the experiment by Kuroda about twenty years ago, using the same CJD mouse-adapted strain that we used in the more recent experiments, and in that experiment he showed a very low rising level of infectivity. Actually, he showed the classical early rise of infectivity in the spleen over the first several weeks, which then decreased to a final titer of about 1.5 logs of infectivity at the time the animals became sick. Coincidentally, the titer of infectivity in blood was undetectable over the first several weeks and then slowly rose to a titer that was approximately the same as spleen at the clinical onset of disease. I don't know of any other experiment where that kind of information was obtained, but at least in that one, that is all I can tell

you.

DR. ROHWER: There is a series of very beautiful experiments by Kimberlin comparing the rise of infectivity in spleen versus brain --

DR. BROWN: Right.

DR. ROHWER: -- after various routes of infectivity but, unfortunately, he didn't look at blood.

DR. BROWN: Other questions for any of this morning's speakers? Yes, Barbara?

MS. HARRELL: I have a question for Dr. Souci. Do you feel that the group that you studied, the hemophiliacs, reflected the typical person who received a transfusion, that they were at high risk for HIV because being hemophiliacs they were all male, and also they had a typical exposure to blood products? And also taking into consideration that HIV has a shorter incubation period than CJD? Do you think your findings were valid based upon your population that you were studying?

DR. SOUCI: I think that what we were really trying to do with the hemophiliac community is to look at a high risk group of individuals. What I mean by high risk is, if CJD is present in the blood supply and if CJD can be transmitted this way, this group of individuals is at much higher risk than you, I or just someone who might get a

blood transfusion. So the idea is that we are looking at the people in whom we would expect to find this if it was in the blood supply, with a higher prevalence than in the general community.

So your point about AIDS having a shorter incubation period is a good point. These people may be being exposed to HIV and CJD at the same time and, of course, the AIDS will cause their demise before the CJD can express itself. But as we continue on, and there are individuals with hemophilia who have escaped becoming infected with HIV but, nonetheless, have had many years of exposure to these factor concentrates and by continued surveillance we are hoping to pick that up if it is the case.

DR. WHITE: Two questions, one to Dr. Weinstein. Mark, when you talked about recalls, I just want to make sure I am correct in remembering that there have been no recalls related to the albumin which is used to formulate products. Is that correct? All the recalls have been because there has been a donor in Factor VIII or some of the blood clotting factors who was positive for CJD. There was not a CJD-positive donor in the albumin which was used to formulate the products. Is that correct?

DR. WEINSTEIN: I believe that is correct. I

would ask my colleagues who are directly involved.

DR. EPSTEIN: For the record, Jay Epstein, Office of Blood. There has been at least one recall. Actually, we classified it a withdrawal, not a recall, of an allergenic product based on the fact that the diluent which was used for injection and was distributed with the allergenic was made with withdrawn albumin.

DR. WHITE: Okay. But that is the only one of that type? It was an allergenic product and no other products have been withdrawn as far as you know?

DR. EPSTEIN: I think that is correct. There have been investigational products that have been used with a specific informed consent after the Agency was informed of exposure to implicated derivatives in manufacturing, but those wouldn't have been identified as withdrawals in any case.

DR. WHITE: A second question, and I am not quite sure who to direct it to, maybe Dr. Rohwer since he got up and provided some data which I am still not quite sure I fully understood, suggesting that blood components might transmit the etiologic agent of some of these disorders, and then got up later and said but epidemiologically there is no evidence that CJD can be transmitted by blood and blood products. I guess the crux of what we are going to wind up

discussing this afternoon hangs in the balance between these two observations. Why is it that you are seeing something experimentally and not seeing something epidemiologically?

DR. ROHWER: I don't know for sure, but let me share with you my perspective on it. It wasn't clear to me when we started these experiments that even if there was infectivity in blood that it would transfuse because it is not clear to me why the infectivity would be in the blood in the first place. Blood doesn't seem to play a role in this disease; it is a central nervous system disease, though maybe Aguzzi is maybe changing our view of that.

But we needed to look anyway, so we did the experiments -- established the model, did the experiments and we see one transfusion. There are still some caveats attached to that transfusion. There were 22 done and only 1 of them transfused, yet, it looks like every single blood contains infectivity in the blood itself because every single blood that we looked at, and there were 7 or 8 of them there, 2 or more animals that came down.

DR. WHITE: And you say that because when you inject it intracerebrally you get a positive result but when you inject it into the blood stream you don't.

DR. ROHWER: Exactly. There is a difference in route, and there may be a difference in the actual form of

the agent, the way the agent is presented to the organism by those two routes. When we inoculated the blood ic, I should also point out we lysed it first. The question we were trying to answer was is there infectivity in here, and my concern was that if it was cell-associated and if it was on some dead-end processing pathway, for example clearance pathway, we could inoculate it ic, it could be there and we still wouldn't see it. When we inoculated the blood by transfusion everything is intact; we are just moving it from one animal to another animal to see whether we could cause this infection. We have seen it once out of 22 times. I am just very uncomfortable with a single datum like that. I would like to see it again.

DR. BROWN: Yes, Gil, you are precisely right. What the Committee will have to wrestle with is the fact that there is potentially an infective agent in blood which has never been demonstrated to be transmitted in humans.

DR. WHITE: Yes.

DR. BROWN: That is the bottom line.

DR. WHITE: I don't seem to have a problem with something being in blood. I mean, that doesn't mean I think it is there but Kuru, BSE, they all have to get from the stomach to the brain. The only way that I can think of that they can get from the stomach to the brain is through the

blood. I mean, it is reasonable to look in blood, but I still have trouble understanding, I guess, why you can see some infectivity in blood and, yet, these products, which are pools of large numbers of donors which might potentially have large amount of material in it, are not showing anything epidemiologically.

DR. ROHWER: The other important variable here is loss of infectivity during processing, and it may be significant and the fractionation experiments suggest that it might be.

DR. BROWN: We are also dealing with very low levels of infectivity. In point of fact, we still haven't even experimentally demonstrated any infectivity in blood during the preclinical period of CJD. We have in rodents but never in humans, possibly because it hasn't been looked for closely enough. By analogy, we ought to find it but we really haven't yet. There is not a single preclinical isolation of infectivity in humans.

Are there other questions? Yes, Linda?

DR. DETWILER: I have a question and a then just a comment. The other route that has at least been shown in animals to get from the gut to the brain --

DR. BROWN: Nerve.

DR. DETWILER: -- is the nerve route. So I think

we can't forget that that is a possibility because Kimberlin really looked at that.

DR. BROWN: And Dr. Diringer also has looked at it more recently --

DR. DETWILER: And another group in Germany, yes.

DR. BROWN: There is no question that the agent can reach the brain through nerve. No question. The question is whether it does in nature.

DR. DETWILER: I do have a question and I am not sure who to throw it out to, but transmission from humans -- and I know that it has not been able to be accomplished in primates by the blood transfusion, but how about intracranially from blood? Humans with clinical CJD to primates? Has that been accomplished?

DR. BROWN: To primates? No, but it has been accomplished four different times in four different laboratories out of about double that number of attempts. There are potentially problems involved with each one of those so-called transmissions or they all may be legitimate, but there are four successful reported transmissions of infectivity into rodents using the blood of clinically ill patients. Larry?

DR. SCHONBERGER: I was wondering if the statement that I make often in talks that I give --

DR. BROWN: Is this a question directed to one of our speakers?

DR. SCHONBERGER: I think Rob Will and one of the international representatives -- that we do not have any case of CJD in a hemophiliac in the United States that I know about. I wonder if that statement is also true internationally, as far as the representatives from England, Canada, Germany?

DR. BROWN: All right. Bob, why don't you start off and then we will ask if Dr. Heino or Dr. Tateishi has any information. Perhaps we will get that information from Maura Ricketts this afternoon. Bob?

DR. WILL: We do not know of any hemophiliac in the United Kingdom who has developed CJD, neither, I believe, within the European surveillance system since 1993 has there been such a patient. But there are caveats to the evidence because the question is whether with hemophilia the mean lifetime survival is less than one would expect normally.

I think the other important point about this, which I think is very important in view of all the surveillance activities that have been started, is that if we start looking systematically for CJD in large populations over a prolonged period of time, we will by chance start to

identify individuals who might apparently be at greater risk of CJD through blood transfusion or through multiple hematological treatments in the past. So I think the interpretation of single cases is very difficult.

DR. SCHONBERGER: Yes. I know Marian Sullivan and I have talked about that in the study of the follow-up of the people who have received --

DR. BROWN: But this is built in though. You look at high risk groups in the expectation -- or potentially high risk groups in the expectation that if there is a higher risk you are not going to have a single patient; you are going to have a bunch of patients compared to a normal population that is not at high risk. So, of course, with one case you can't build a case.

DR. SCHONBERGER: I would like to emphasize if the number is still zero, which is what I am hearing for hemophilia patients and severe hemophilia patients get exposed to many different lots of the Factor VIII products which, we have heard, come from 30,000 or more donors, by the time a hemophilia patient, at a very early age, five years old, say, based on calculations that we have heard today and calculations that Paul Brown gave to Congress recently where they are talking about maybe a 50% chance of any lot that has 30,000 or 100,000 depending on what you

consider the incubation period to be for CJD, that you have about a 50% chance that their lot has been contributed to by a person who will subsequently get CJD. So, essentially, the severe hemophilia patients at least can all be regarded as potentially exposed and, yet, we have just heard that nowhere in the world have we had a case of CJD in a hemophilia patient, who would not have to live beyond 20 years old, say, to meet the incubation periods that we have seen for all these other problems that we have been talking about with this disease.

DR. BROWN: Professor Tateishi, has there been a case of CJD in a hemophiliac in Japan or any other patient with multiple receipt of blood transfusions?

DR. TATEISHI: Tateishi, from Fukuoka, Japan. I had once an autopsy, a sporadic CJD patient, and took a clot from the heart. I inoculated it intracerebrally into the brain of mice, and some mice developed the disease after a long incubation period. I don't remember the exact incubation period, but it is near 1000 days after inoculation.

DR. BROWN: I'm sorry; was that a sporadic CJD who was a hemophiliac? The question is have you seen CJD in Japan in any patient with a coagulation defect or hemophilia?

DR. TATEISHI: I have never seen such a CJD patient, with hemophilia.

DR. BROWN: Thank you. Maura, why don't you tell us?

DR. RICKETTS: None.

DR. BROWN: None in Canada? Yes, Dr. Souci?

DR. SOUCI: I was wondering if I might say just one thing about looking for cases among persons with hemophilia? The point about finding one case, as one of the people mentioned, if you look long enough and hard enough you might find one but you would not expect to find a case of CJD in a person with a bleeding disorder who is less than the typical sporadic case age. In other words, if we found a case in someone who was 60 or 65 years old, that is different than if we found one in a person with a bleeding disorder who was 30.

DR. BROWN: that is a good point. Bob?

DR. ROHWER: I wanted to come back to Dr. White's question and just clarify one thing. That is, I am not saying that there is no risk associated with blood and blood products. The point that I was trying to make in that last bit there was simply that you can't differentiate the risk on the basis of identifying the occasional CJD patient; that all those plasma pools have the same risk regardless of

whether we see a case or not because the majority of the exposure is not coming from those few cases we see, it is coming from a large number of cases we don't see and we have no way of seeing.

DR. WHITE: No, I understand that.

DR. ROHWER: But there still may be a risk.

DR. WHITE: No, I understand that, but the implication from your comment is that all products are, therefore, at risk and if we are not seeing anything, therefore, there is no risk or very little risk.

DR. ROHWER: No, what I am saying is the risk must be very small, and that is the message from the epidemiology but I am not saying there is no risk. And I wouldn't be at all surprised that as people look harder and harder and harder eventually they will find a case.

DR. WHITE: I agree with that.

DR. ROHWER: But it won't change the risk.

DR. WOLFE: Bob, I don't think it is fair to say that you are trivializing the risk by adding in all the people who are subclinical and infected, but I think in equating them as equal with cases the point that you and others have made earlier is that it is certainly likely that the blood infectivity level goes up as someone gets closer to getting -- we don't know that. It is the most plausible

thing. Even though there is no very good experimental evidence, it is most plausible that the amount of infective units in the blood are going to be higher as one approaches or actually gets to the point of having clinical disease. Therefore, using as a signal of problem those people who have had, after donation, clinical disease, particularly ones who donated within whatever period of time, and those are going to make a much larger contribution to the total pool of infectivity in the 20,000 or 30,000 units you are talking about.

I mean, I am not disagreeing with you. I am just saying that there is a waiting phenomenon that has to go on there because --

DR. ROHWER: There may or may not. Actually, the experimental evidence, and we haven't presented that data here but if you look at what has been done in the past and include the experiments that I presented today, we did look at preclinical as well as clinical disease in the ip model and we didn't see any difference in titer in animals taken 40 days after inoculation and taken at clinical disease, 140 days later. And that is consistent with experiments that Heino Diringer has done in the past, and Pochiarri actually saw in the same model a decline in infectivity as it approached clinical disease whereas Kuroda saw an increase.

DR. WOLFE: In the blood.

DR. ROHWER: This is in the blood, right. And that is on the basis of incubation time in those other experiments. So it is not real clear, and those differences are subtle enough that they may be just statistical fluctuations. As a consequence of that, I don't think we can really say, and it definitely is not true that there is a huge change in infectivity titer between preclinical and the end-stage of disease.

DR. WOLFE: These are in animals whose disease arises from inoculation as opposed to what we are mainly talking about, the human disease --

DR. ROHWER: There you have identified a major difference.

DR. BROWN: Let me conclude this morning's session, therefore, by saying that we will have that information on a limited scale but it is to going to be in time for us to consider it. We will have it because the only human beings in which this kind of information could possibly be made available are patients' members of families who carry lethal mutations and who are healthy. In fact, we have a small number of such specimens and they will, before the end of the year, be inoculated into a variety of rodents, transgenic mice and primates.

DR. WOLFE: Which will be very helpful.

DR. BROWN: Yes, but unfortunately we are here today. It is now 12:42. I would like to reconvene the meeting as scheduled, at 1:30. So we have 45 minutes for lunch. Thank you.

(Whereupon, at 12:42 p.m., the Committee adjourned for lunch, to reconvene at 1:35 p.m.)

AFTERNOON SESSION

DR. BROWN: I think with Peter Page and Bayer, we probably would have two people who could give us the answer to a question that was deferred until now. I will wait until Peter gets here to ask him.

We will not need today, assuming I get an answer to the question that I am about to ask, a secret session. So you will be able to sit where you are sitting for the duration. Is Peter Page here now? If not, we won't wait any further then. We will delay that question until after the next presentation, which is by Maura Ricketts, from Canada, who will focus on the Canadian approach to withdrawal and risk assessment in general. Maura?

Risk Assessment: Potential for Transmitting CJD by Human Blood, Blood Components, and Plasma Derivatives

DR. RICKETTS: Thank you. I will start by thanking the Committee for the opportunity to come and speak to you on this interesting subject today. I realize very well that I stand between the Committee and its deliberations; I will try and keep my remarks to the point. However, I did have a little problem in ordering my slide set. I did receive 20 slides. They were duplicates of each other. So maybe that is God's way of ensuring my presentation is kept a bit shorter.

I have been asked to talk about risk assessment and risk analysis regarding this particular subject area because I think Canada is probably one of the most conservative countries on this subject, and I think that it is worthwhile spending a few moments discussing why it is so conservative in Canada.

I think I want to start by saying that our policies in Canada don't discourage us from including the opinion of the public in decision-making. That may seem not necessary to say but, in fact, in general as scientists we have a tendency to make our decisions based on scientific information, using rates, and prevalence and things and, in fact, the public does not always use this kind of information in decision-making. In fact, the public is involved in a particular paradox in that the longer we live, the better quality our lives are, the less we are willing to risk what we have. This paradox often means that we are unwilling to accept risks that are even very, very small, even theoretical and we have to be prepared to understand that need on the part of the public if we want to develop good public policy.

I think this paradox includes some bizarre --frankly, I have to use the word bizarre -- things, the fact the same members of the public who will tell you I will

not tolerate being exposed to the risk of CJD from blood will also get into their car and not do up their seat belts. But it is not up to us to judge those matters, simply to recognize that they exist.

(Slide)

In risk perception there are two really important factors from the public's perspective, and they are called dread and unknown. I think many of you have seen cognitive risk maps and are aware that these things exist. CJD in blood policy development is haunted by both elements. It is a dreaded disease and there are enormous numbers of unknowns.

Another important issue that we have had to deal with in Canada is the fact that there has been an important loss of public trust. To give you an example of how trust works in risk assessment, I would point you to the risks of radiation injury in that the nuclear power plant industry is completely mistrusted regarding their risk assessments and, yet, a doctor can order an x-ray for their patient and be completely trusted in this matter. These are exactly the same risks. The source of the recommendation is different; the level of trust is completely different.

In Canada the blood industry has taken an enormous hit in the area of trust. The HIV and hepatitis C epidemic

did not leave the United States untouched. And trust is an important issue for us right now, and we are struggling very, very hard to restore public trust in the blood system. We are doing that partly by being very conservative in our opinions. But partly, I have to confess, it is much easier to work in an environment of trust and we believe it is worthwhile investing in it.

One of the most important tools in restoring trust is public involvement in our committees and the use of public interest groups in our committees. Those committees push us strongly towards extremely conservative opinions. We have used public involvement very well, and one issue that I didn't intend to talk about but I will mention briefly, with the Committee's permission, is that we held a consensus conference on recipient notification following the receipt of blood from someone with CJD. That consensus conference, which was well attended by the public, did not conclude that every recipient of CJD source blood should be themselves personally informed. They did conclude that everyone of those people had the right to the information but they also had the right to not get the information leading to the necessity on the part of hospitals to develop large registries so that patients could contact them and find out if they were exposed, plus, also driving those

communities, hospital-based communities mainly, to seek public opinion in making the decision for the community, that is, a community-based decision-making process.

Finally, the Krever Commission Inquiry in Canada has altered the way that we do business. I wouldn't be in my current job right now if it wasn't for the Krever Commission. The Division of Blood-Borne Pathogens is only two years old. Recently, the Krever Commission Inquiry was informed by the supreme court of Canada that they could name names. That is, people who seem to be responsible for some of the problems that arose from HIV and hepatitis C transmission in the earlier part of the '80s are going to be named in the Krever Commission report when it comes out. I think that for public policy makers this is a very intimidating piece of information for us.

(Slide)

I will move on more quickly from here. Risk assessment in Canada, as in the United States, is based on two processes. Risk assessment, the first part, is the collection and analysis of health data. We have been seeing an awful lot of that data today. And the development of options for managing risks, and we have been hearing about some of those options today.

The second part of it is risk management, which is

the selection and implementation of the strategies to address risk. I will point out to you that I work only in surveillance issues. I only do the risk assessment component. In the next slides I am going to talk about that component of my work.

(Slide)

I need to remind you that risk analysis and risk assessment is not one tool. There are many different types. For example, chemical risk analysis involves concepts like no observable effect limits, and so forth. Qualitative risk analysis is things like will we have harm come from acid rain? The kind of risk analysis that I do is epidemiologic risk analysis, and much of what we have been seeing over the last day has been epidemiologic risk analysis, and only epidemiologic risk analysis.

(Slide)

What I want to talk about at this point, without providing any of the details of the currently conducted studies because they have already been beautifully reviewed and there are wonderful publications and you can read the if you wish, I want to talk about the uncertainty inside these that have led us to the point where we acknowledge a theoretical risk. It means that I will spend two or three slides talking about the weakness in the existing

epidemiological studies. For instance, Dr. Sullivan's presentation this morning is not included under this caveat. I mean the older published case control studies plus some of the difficulties in interpreting the data that comes from surveillance systems.

The first think that I want to talk to you all about is the issue of asking people questions about their history of blood exposure. If you look at these studies, you find that the papers appear to indicate that between 11% and 25% of people have been exposed to blood, but these histories were taken by asking family members whether or not those patients had received blood and that information is simply not accurate. In Canada, when we have done look-backs only about 60% of people were themselves aware that they had received blood transfusions, and only 75% of parents knew that their children had received blood transfusions.

In case control studies, when you create these relative risk ratios you are comparing the rates of blood exposure between those who have CJD and a group of controls. It has been mentioned this morning about the weakness of using hospital controls. It is Carl Berkson's bias. It is an important weakness and you have to be very cautious in interpreting those studies. We know from Canadian data that

in one year about 6% of hospitalized patients will receive blood and only 1% of the population will receive blood in that same time period. So hospitalized controls are not appropriate controls for these studies.

(Slide)

So, in answer to the question is the history of blood exposure accurate, the answer is probably no, it is not accurate. This is not a small problem from an epidemiologist's perspective. You may say, oh, well, the cases and the controls were both asked the questions in exactly the same way; it is just some kind of random misclassification. No. This kind of misclassification skews the results towards no. It systematically makes it unlikely that you will find a difference between the two populations and it must be avoided.

(Slide)

Now I want to talk about the history of blood exposure being valid. That is, my question as I phrased it was, was the blood coming from someone who eventually developed Creutzfeldt-Jakob disease? Because, in fact, really we don't care if the person received blood. What we want to know is did they receive the blood with the agent of CJD in it. Obviously, the whole incubation period question that came up this morning is very important here. The

calculations that were done around 25- and 4-year incubation periods would alter tremendously our estimates of how frequently people are exposed to blood.

I am not personally convinced that we have enough information to make declarative statements about the length of the incubation period inside human beings, nor the extent of infectivity in the blood during that whole time period, particularly since almost all the cases that we are dealing with are not iatrogenic. Those mice are iatrogenically infected. They are sporadic. The infection begins in the brain. How does it get out? How does it leak out? What is the natural history of the disease in the human being? I don't think that we have that information, although I hope the Committee will review it and it is possible that Dr. Prusiner's mice will actually answer some of our questions on this.

One of the problems that arises from misclassifying people as exposed by simply asking them what the history of the blood is exactly the same problem as I described in the previous slide. It skews the results towards no. So that epidemiologic studies, such as Dr. Sullivan's and Dr. Schonberger's continuing studies which will attempt to find out whether or not there was some reason for being suspicious about CJD in the blood, will be

extraordinarily important and we must continue to do these studies.

(Slide)

While we do these studies we can't forget the importance of codon 129. It would appear from the human growth hormone studies that codon 129 could predict either susceptibility or incubation period. I am not sufficiently prepared to make a declaration. I think it could actually be either. However, if only a portion of the population is actually susceptible to CJD within a time frame that we can recognize, and admittedly that is probably half of the population of human beings, we have ended up misclassifying cases as exposed if we don't know the codon 129 status. So when we do these investigations we must get information about codon 129, and we may find other markers as time goes on.

(Slide)

Gee, I haven't been looking over my shoulder to make sure you guys you have the same slide as I did. So if any of them didn't make sense, I know the reason for it but you don't.

I want to talk for a moment about the concept of multiple causes of CJD. I think everyone in this room is ready to acknowledge that CJD has multiple causes to it,

making it more like a disease like lung cancer. Most lung cancer is caused by exposure to tobacco smoke but some of it is caused by exposure to background radiation, radon and certain occupational exposures. The initial epidemiological studies that attempted to find those relatively rare causes of a relatively common disease were extremely difficult to conduct and extremely difficult to understand the results from them.

I don't think that blood products can possibly account for all cases of CJD, with the exception of the scenario in which you consider perhaps vaccines to carry a real dose of the CJD agent. The fact of the matter is that if blood and blood exposure approaches 20% in people who have CJD, that is probably the absolute maximum. I, frankly, think it couldn't even be that high. I believe that it is probable that blood is a rare cause of CJD.

But I do want to mention to you that in population statistics it is very difficult to identify rare causes of diseases and nvCJD, 22 cases, are only deforming the statistics in the United Kingdom now. So general population statistics are not a good way of looking for rare diseases either. Case control studies are generally considered the recommended method for finding the size of risks for rare events, but they are really not that good at looking for the

existence of the rare event in the first place. The best way to find rare events is to go and look for them.

(Slide)

I want to address this question, why haven't we found any cases of CJD caused by blood, because we haven't. Again, again, as has been pointed out by other speakers, we are out hunting for them; we are not finding them. Well, we are not concluding that they are linked. In Canada, a donor from Vancouver, that person's blood was pooled. There is a person who developed CJD in the cohort of people who received product from this person, but they developed their CJD in less than 8 months. Everything about the case was completely consistent with sporadic CJD and we don't believe that the two things are causally linked.

So the first answer to the question might be that there aren't any cases; that this doesn't happen at all. But the other answer to this question I think is more likely, and that is that these cases, if they happen, are going to be very, very hard to find. I want to remind people that if the incubation period is very long for CJD, it is going to be extraordinarily difficult to find them. It is not unreasonable to assume that the incubation period will be long because we have evidence that if there is a dose of CJD in blood, it is probably very low and dose and

incubation period are linked.

So we know that about half of blood recipients die within about 5 years. There is one population study on this. There are competing causes of death in that population, losing the study population. From the perspective of an epidemiologist, all my population that I want to study is disappearing. With the hemophiliac population, as was brought up earlier, competing causes of death are very important. If the incubation period exceeded 30 or 40 years it might be actually impossible to find it inside hemophiliac populations. And incubation periods that are very long allow populations of people to move away from their original exposure site. So you don't have one doctor seeing two or three cases in the hospital, as happened with CJD in Spain with one hospital having four cases reported in a year. Instead, everybody moves away. We live in big countries, and people forget about what their exposures were. So long incubation periods are a big problem for us.

(Slide)

So here is the epidemiologic bad news: We have a rare disease with a rare exposure, and I will acknowledge all the earlier arguments this morning that this exposure might not be all that rare but still I think we might want to consider that it is a rare exposure when we do our risk

assessment and include it in our models.

We have a probably long incubation period. We have no test for the true exposure so that we can't link cohorts of people and actually prove that they all got their CJD from the same source, like we do with HIV.

We don't even think that all people are uniformly susceptible to this disease. Iatrogenic disease is difficult. I have written "cannot be distinguished," but it is difficult to distinguish from sporadic diseases. By this, I actually mean to the extent that if a person presented with cerebellar signs a fist would come down on the table and declare this case is iatrogenic. And I don't believe, although I would welcome comment from the clinicians, I don't believe any of the clinicians would be willing to make that statement.

(Slide)

There is epidemiologic good news. That we that we -- not we because I have only come on this scene recently, but others in this room very successfully detected some very important outbreaks when they were quite rare. Dura mater, for instance, was clinician-initiated response, the detection of three or four cases in one hospital site. Human growth hormone was detected. Although this is a monitored cohort, that is, a group of people who are watched

very closely by one group of clinicians, it was detected. You would think the same thing could happen in hemophiliacs if it was occurring there.

With the surgical instruments there was temporal proximity. That is, the cases occurred relatively close in time to their exposure and that makes life a lot easier. With nvCJD there were some definite helps that were also present in the other diseases. Novel neuropathology was extraordinarily important in recognizing that something was going on, but most important was the epidemiologic marker of youth. As was mentioned this morning by Dr. Souci, the occurrence of CJD in a 30-year old hemophiliac would probably send chills down most people's spines.

What I wanted to say with these two slides is that the capacity of epidemiology to detect rare events exists, and it does give a certain degree of confidence that if this is happening, it cannot be happening very often.

(Slide)

I don't want to discuss the animal data at all. It has been gone over extraordinarily will and I am sure I would make some kind of a mistake. But I do think that we are asking a number of important questions about whether or not blood in a naturally infected person, by which I mean someone with sporadic CJD -- does the agent squeeze out of

the brain somehow or other, get into the blood, and if it is in the blood can transfusion, as an action, actually lead to the transmission of the disease, or does prion, you know, just flow around in the blood stream, snuggle up inside the spleen and do no harm? I think these questions are being addressed by other researchers and it is very important that they be answered.

(Slide)

In our risk analysis here we are dealing with uncertainty and variability. We know only that the risk is between 0-1, and we do not know which it is. But it would appear that the evidence is narrowing the boundaries on this; that it is likely that it can happen but that it does not happen very often. So we are gradually narrowing the boundaries on this risk assessment. And risk assessments should do much better than they are doing currently, but with the studies that are currently being done I am very optimistic that we will have good information.

I will mention that characteristically governments have a tendency to feel that if a risk has not been identified there is no risk. If you haven't got a problem, why are you talking about it? Inside my own government at the same time, we are no longer happy with that kind of attitude and we are being asked and are trying to be

proactive in addressing these kinds of problems.

(Slide)

Finally, given what I have already said, I do believe that we must continue to invest heavily in this research area in order to answer this question. If we fail to answer the question well the harm that can be done to the population and to the blood industry is quite enormous. If we cannot perfectly quantify risk, we can still continue to quantify the protection that is being given by the measures that can be taken to reduce risk. There were presentations this morning about reducing risk.

The slides that are missing are right about here. Some of the techniques that are being used to minimize risk include issues like donor screening; include the performance or withdrawals; include the various decontamination and sterilization procedures that can be applied to a living tissue like blood; include the manufacturing processes that were described earlier I the day and are being addressed.

I think that it behooves us to put those kinds of information in the public eye and to attach numbers onto them so that we can actually build our risk assessment models better. I personally find it distressing that it is so difficult to look at this information and include it in our risk assessment in Canada.

I think that, in fact, I will stop right there. Thank you very much for your attention.

DR. BROWN: Thank you very much, Dr. Ricketts. I have one comment and one question. There is no question that the agent can be in blood. I don't think we should even argue about that any more. It is.

One of the things that hasn't been mentioned today, and we sort of forget about it because it is not on the table, is that a patient who is dying from CJD and dies, and I am talking about a human patient now, has demonstrable infectivity in many organs of the body, not just the brain: spleen, liver, lymph nodes, lung, heart, kidney. How does it get there? Well, it gets there through the blood. We don't know when the blood is infectious but it is not traveling around the body in peripheral nerves.

Also, there are some very interesting experiments ongoing from Switzerland by a chap named Adriano Aguzzi, and he has demonstrated, for example, the necessity for the PrP protein to be present in a mature B cell. You need mature circulating B cells in order for infectivity to reach the spleen. I don't want to go into details, but he has taken mice without PrP, that is the so-called null mice, knock-out mice, irradiated them so that they have no bone marrow and then transfused or given these knock-out mice normal bone

marrow and then has tracked down the kinds of cells that the marrow is producing, and has found that in order for infectivity, if you infect an animal, for example, in the foot pad, you need a mature B cell to carry that infectivity to the spleen. Without a mature B cell you find no infectivity in the spleen -- one more point in favor of the fact that this agent does exist in blood.

The question I had is probably really a question to Dr. Will. My understanding of the European surveillance study with respect to the controls, and I may be wrong which will be embarrassing because I am a consult to your committee, but I thought most of those controls were not hospital patients but were very frequently relatives of the patient who happened to be on the wing in the hospital, or other people who weren't actually hospitalized. Am I wrong or am I right?

DR. WILL: Well, I am afraid I am going to have to embarrass you, Dr. Brown.

(Laughter)

The situation is that in all countries we tend to use hospital-based controls. I think the confusion may lie in the fact that, of course, it is very difficult to interview the patients directly because they are so ill with Creutzfeldt-Jakob disease, and in order to obtain comparable

information of the same quality we tend to interview the same degree relative in the controls. But it is still hospital-based control cases.

There is an exception to that. In France, because of the practical difficulties sometimes, they have been interviewing relatives directly rather than hospital-based controls, and that has resulted in similar findings.

But I do understand the difficulties with interpreting the case control study but I do think, nonetheless, in view of the various precautions we have taken about looking at different epochs in the past, etc., it is difficult to dismiss this evidence completely.

DR. BROWN: Are there any questions now for Maura, who is our last scheduled educator? We had an opportunity to ask questions of all the other ones. Are there any questions that anyone has for Maura? Yes?

DR. LESSIN: What is currently the actual practice in Canada with regard to the things that you mentioned? Risk assessment in donors, regulations or guidelines regarding processing etc., etc?

DR. RICKETTS: It looks a lot like in the United States. If you want details of it, Dr. Doug Kennedy is in the audience and can provide you with the exact details. It looks a lot like the States, although we are probably more

conservative on the families and we would like to do gene sequencing whenever we have a family member. Would Dr. Kennedy like to speak to this issue? Would you like more detail, because he is here?

DR. KENNEDY: I am not sure that I can add very much to what you said, Maura. It is basically very, very close to the U.S. policy. I think there are very few significant differences between them even in the context of family members, though we do tend to do a fair bit of genomic analysis.

DR. ASHER: Have you addressed the issue of secondary products?

DR. KENNEDY: No, we haven't, other than that we have had some discussions with some learned colleagues. We were obviously concerned about it as well. I am very happy to be here to hear the discussion today.

DR. WOLFE: Short of the question of secondary recalls though, have your policies on recalls of just the primary whole blood and blood products been similar to the United States?

DR. RICKETTS: It is extremely close, yes. It is very difficult for us to have a different policy.

DR. SCHONBERGER: I just wanted to make a comment on the short incubation versus long incubation period

question with regard to hemophilia patients. It is true that we get long incubation periods for Kuru and other diseases, but not without some of the short incubation cases showing up as well.

DR. RICKETTS: Yes.

DR. SCHONBERGER: So it would be the first time that we would only have one that showed a long incubation period.

DR. RICKETTS: Yes.

DR. SCHONBERGER: Secondly, the hemophilia patients, and I assume you accept the statistics we heard today that, given all the lots that a severe hemophilia patient would be exposed to at a very early age, statistically, even though we haven't pinned down where they have been exposed, a substantial proportion of hemophilia patients would be exposed, say, before five years of age or something. Is that fair?

DR. RICKETTS: Yes. On the incubation period question, if you used HIV as an example, 2% in 2 years, 50% in 11 years, you will see the 2% cases. That is how you find HIV transmission from a dentist. You count on the short incubation period cases to give you that. In this case, I am not confident that we know what the incubation period would be in blood, and a short incubation case may be

10 or 15 years. It only makes it more difficult. It is extraordinarily reassuring that none have been found, but it does make it much more difficult and in asking yourself the question could we have missed the cases, the answer has to be yes.

DR. SCHONBERGER: Right.

DR. RICKETTS: The incubation period goes like to 40 years and competing cause of death is extraordinarily important.

DR. SCHONBERGER: Let me make two other points. One is that the human growth hormone experiment uses a route subcutaneously which, according to my understanding of Rohwer's data, would be less efficient than intravenous. So the intravenous route -- because there are many people who get blood as a child as well, including sickle cell and so on --

DR. RICKETTS: Yes.

DR. SCHONBERGER: -- I mean there is a lot of blood that is given to children. In other words, I am looking for the cases in that teenage period or early 20s which would stand out. What I guess I am saying is that at least with the incubation periods that we have observed to date, say, with the growth hormone situation which is probably one of the very lowest contaminations that we can

observe, at least in the sense -- and Paul can comment on this because he has taken lots that have been implicated in human transmission and inoculated that into primates, which are considered a very sensitive animal, and the primates, at least from the specific lots that we have already identified from human cases, have not come down. He did get, I guess, one transmission from a lot that I don't think is as clearly associated with the human case. But the point is that we are dealing with an extremely low dose in the human growth hormone situation, and he inoculated that in a route that is going to be less sensitive than what is in the blood situation. There, we see cases, you know, certainly within the 18-year period. Although it is true we may see cases going on for many more years, we still get those early cases.

DR. RICKETTS: You simply need to satisfy yourself that blood and human growth hormone are equivalent. If you can do that, then you can use the incubation period and you can make all your models based on that incubation period. But until you can do that -- and maybe someone wants to say that they are satisfied they have that information now, you have to ask the question if it is missed because of a longer one, because of dose, not route.

DR. BROWN: Well, as far as I can tell, there are

three relevant pieces of information. One is the growth hormone story, peripheral route, intramuscular or subcutaneous, with incubation periods ranging from a few years to 30 years.

The second relevant piece of information comes from the story of Kuru, also an environmentally acquired form of these diseases, and the incubation periods there can range up to 30-40 years. They can also be as short as 4 years.

Actually, those are the two major bits of information. So maybe the incubation period data from these two examples is applicable, not only to blood but to other peripherally acquired infections. It is the best information we have. I don't think we are going to satisfy ourselves that it is equivalent. That is always a dangerous word. But I think that it is reasonable on the basis of these two experiences to expect incubation periods to be in this range.

DR. SCHONBERGER: That is basically the point I was trying to make. I can't disagree with that --

DR. BROWN: The third piece of information is the presumed BSE origin of nvCJD in which the incubation period is likely to be around 10 years because the exposure would have occurred in the mid to late '80s and now we are seeing

cases in the mid to late '90s.

DR. ROOS: Paul, how about the infectivity in the growth hormone samples? Can you say anything about it? Do you think it is comparable to the low infectivity data that we heard from Bob?

DR. BROWN: Just no information. You know, we inoculated 79 or 80 different lots of growth hormone. Only 1 lot transmitted, and that only to 2 or 3 monkeys, and the incubation period was 5 years, which doesn't really tell us too much. It is a little longer than what you would expect from sporadic CJD which had a mean of 2 years. There are cases of sporadic CJD inoculated into the same species of monkey with incubation periods of 5 or 6 years. So no information on the dose but it has to be small, just as the amount of infectivity left on a sterilized, washed, cleaned electroencephalographic needle which 2 years later, having already caused disease in 2 patients, was then implanted in the brain of a chimpanzee and still caused disease. So in terms of the number of particles, we don't need very many and we are certainly dealing with low levels of infectivity in the blood but I can't give you a number.

DR. DETWILER: I have several questions for Dr. Ricketts. Is CJD reportable in Canada?

DR. RICKETTS: No, it is not. We have actually

addressed the issue of whether it should be reportable and we remain unconvinced that it will improve our reporting. There may be other reasons for moving towards reportability but until we get evidence that doctors are not thrilled to report their cases that families will insist that the cases not be reported, we would rather use a fully voluntary system. If we did find that we don't get good reporting, if we find that family members refuse to cooperate, we will ask for compulsory reporting at that point as a kind of medical emergency but we would have to justify that. It is reportable in France, by the way, unless somebody can contradict that.

DR. DETWILER: Another follow-up. Do you assume that there is some under-reporting then?

DR. RICKETTS: Oh yes, absolutely. We will conduct a study similar to that already conducted by Dr. Schonberger in which we will hunt and seek cases being reported by clinicians. At the same time, we will find all of the cases that are reported through death certificates. We will compare those data and calculate reporting completeness. If we can conclude that we can use death certificates, we will because it is cheaper but we wouldn't be able to get all the other wealth of information we need. So we are quite keen on doing a case by case search at this

point.

DR. DETWILER: Then one final question, if you assume that it is under-reported as far as your clinical cases and there is incubation feeding into your blood supply, did you discuss the fact that withdrawals actually might leave a false sense of security to the public receiving blood? And is there any action being taken?

DR. RICKETTS: There is no action being taken. Certainly, it has been mentioned. The problem would be could you honestly stop doing something that offers any insurance, given that you have initiated it? I think that that is the tough part to do. But I agree with you, the false sense or security and public education on risk, on theoretical risk, labeling is another whole day's discussion.

DR. DETWILER: Do you educate the public that there may be an inherent risk for any donation then, or any recipient?

DR. RICKETTS: We do not at this time but we are moving towards labeling.

DR. DETWILER: Thank you.

DR. BROWN: In other words, sort of every unit that goes out says this may, you know, cause disease?

DR. DETWILER: I am not suggesting that. But if

there is that much major concern theoretically.

DR. BROWN: I have to tell this because it is so good. I went to a military hospital several years ago before I had a tooth procedure and they gave me a sheet of paper to sign off on. There were any number of possible complications that I had to agree might occur. Then as I got down towards the end of the page, it indicated that there might be serious paralysis of the jaw, and the penultimate line was death. Then the ultimate line was "other."

(Laughter)

That is really informed consent.

DR. SCHONBERGER: Paul, one more question for Dr. Ricketts. I was wondering how long -- it may not be a fair question but how long would you have to conduct your surveillance and not find any documented cases that you would feel comfortable in reversing the policy that is in Canada?

DR. RICKETTS: Yes, it is an awful question because you have been involved in the calculations on the statistics. If you are looking for a 1/1000 kind of incidence you are talking about 10,000 observations. It is extraordinarily difficult. I don't know what the answer is for me, although as I have mentioned to other people, the

woman who actually runs these studies is pregnant and we actually think that her child will be able to continue. In fact, it could be possible that a 30-year study would be required to detect such a rare event, and one should decide if that investment is a valuable investment.

DR. BROWN: Other questions? Yes, Leon?

MR. FAITEK: I would like to address this to Dr. Will. The new-variant form of CJD was just mentioned very casually. Could you explain, first of all, what it is and how it affects the discussion that we are having here today?

DR. WILL: I just mentioned it in passing for the sake of completeness so the Committee had the full information that I had available to me coming here. The reason I mentioned it is that there is concern in the United Kingdom about blood supplies that might be derived from cases of nvCJD. The reason for that is that it is possible that this disease is due to a different type of infectious agent, different strain of agent causing other forms of CJD. If that were the case, it is possible that this strain of agent might have a different tissue distribution and could, for example, have more infectivity in blood than classical and other forms of CJD. That is a concern that we have in the United Kingdom and I thought I would mention it to the Committee.

MR. FAITEK: Is there any evidence for that, that it might be more infectious?

DR. WILL: No, there is no direct evidence at all. This is a theoretical possibility.

But what I did put up was a slide of a tonsil which does contain lymphoreticular tissue, which is apparently important in many of these diseases and replication of agent. It is also associated quite closely with the blood system. What I was suggesting was that at least in the very small numbers of cases in which we have information it looks as though the amount of staining in the tonsils of nvCJD is significantly higher than on current evidence in classical CJD. The implication of that could be that there might be more infectivity in blood in nvCJD. But there are a number of steps to this argument and I think it is still a hypothetical argument, but I think it is an important issue for us.

DR. BROWN: To push you just a bit further on that, have any of the new-variant cases been looked at for the presence of PrP detectable in other organs at autopsy?

DR. WILL: Yes. That is a very important question. I am a neuropathologist, but we have been looking at spleen, for example, in nvCJD and lymph node. There is limited amounts of tissue. We need to, of course, compare

the results of this investigation with classical CJD. One of the difficulties with that is that I think on occasion we have seen some PrP staining occasionally in spleen in classical CJD. Although there is, indeed, PrP staining in nvCJD spleen, it is very difficult on the current evidence to suggest that there is definitely a distinction. There is a suggestion that there may be but we simply need more information.

DR. BROWN: But, in any case, it is certainly not overwhelming. You haven't got new-variant spleens that are brown with PrP and a trace in sporadics.

DR. WILL: Well, I don't think that is the case on current evidence but, as I say, we need a lot more control and new-variant information to be able to be sure about that.

DR. BROWN: Leon, were you going anywhere with that question?

MR. FAITEK: Yes, I just wanted to know if there was another possible infectious agent that we should be looking for.

DR. BROWN: Yes, it is the same infectious agent. It is a question -- well, when I say it is the same infectious agent, it belongs to the same group of infectious agents. It is not like agent X. It is a spongiform

encephalopathy, and the issue was whether or not the strain that is causing nvCJD has different properties within the group. But it is not like comparing, say, flu or polio or parvovirus 19. It is still a spongiform encephalopathy. Ray?

DR. ROOS: I have another question, and that is whether this information is going to impact policies with respect to blood products in Britain with some of the same concerns at our table at present.

DR. WILL: I am not in a position to comment on that because I am not on the relevant committees that would make this decision, but I am sure, in fact I know it is an issue that is being discussed actively and continues to be discussed actively at present in the United Kingdom about whether should actively be done about that, and if so, what. As I said, I think it is an issue that is really under a great deal of discussion. We have only 21 cases of nvCJD in the United Kingdom. Although each one, of course, is a tragedy for each family the numbers are relatively small. My own suspicion is that if there were an evidence of increasing numbers of cases, which there is not at the present, then that might influence such decisions.

DR. SCHONBERGER: Mr. Faitek has opened up an interesting --

DR. BROWN: I don't think we want to get really into this detour --

DR. SCHONBERGER: I know, but one of the frustrating issues in this whole area is the difficulty in doing something effective easily to protect against this theoretical risk. Since you raise the issue about the nvCJD which, in my mind, would be the risk of greater concern because it is an emerging new problem, and I have often argued with people who were involved in setting up the recall for the sporadic CJD cases, as Rohwer pointed out, the sporadic CJD situation has been around for years and years, is not a new situation, and all the epidemiologic data that we are talking about is really relevant to the sporadic CJD that has been around. All that epidemiologic data, however -- at least there is a greater question about its relevance with regard to the new-variant because it is something new. Your raising this issue makes me want to ask the question is there any thought, or do you have any suggestions, Rob, in how one could screen donors or prospective donors in any kind of effective way to reduce the probability that such individuals would be donating blood in your own country, and perhaps it could be adopted elsewhere?

DR. WILL: I think that is an extremely important

question, and I do agree that one of the difficulties is that we are not sure the epidemiological evidence we have in classical CJD is applicable to nvCJD, and because it is a new disease, and I firmly believe that, it will be many, many years before epidemiological evidence would be informative if there is a long incubation period through a peripheral route with low dose.

So it is very important actively to institute mechanisms of determining the levels of infectivity in blood through animal experimentation, for example. But, again, that may involve some delay. So I think it is fair to say that there is very active research going on at present to try and determine whether sensitive markers for the presence of the abnormal form of prion protein could be developed in peripheral blood, which would have implications if it were successful not only for nvCJD but for all forms of CJD.

DR. WOLFE: It is I think quite ironic that in your country a well-documented source of CJD, namely dura mater, has been effectively banned, except for the rare instances where someone is doing it, and in this country we have not but, conversely, we have engaged in a number of recalls of blood and blood products here and you haven't.

I am thinking of the very nice, clear presentation by Dr. Ricketts on issues of public trust and public

involvement, and I guess I am wondering how Britain grappled with the issues, which must have arisen even though they were concluded in a different way, of should we recall blood? Should we recall blood products? And so forth. I mean, I can't imagine the issue didn't arise, and how was it disposed of, or what happened there? I mean, why is it different than Canada or the United States, given that on this other issue you have taken a much stronger position than we have?

DR. WILL: I can't comment on the mechanisms by which decisions are made about blood and blood products because I am not involved with that directly.

DR. WOLFE: But as a member of the public?

DR. WILL: As a member of the public, I would turn the argument on its head, myself. I find it very difficult to understand when we are talking about a theoretical risk in relation to blood and, unlike Dr. Ricketts, I don't believe that there is good evidence that there may be individual cases related to blood. I don't think we have any evidence of that at all.

I am concerned, of course, that the issue of withdrawal of products may have an impact on health in another way, and I am concerned that systematic surveillance will identify very much larger numbers of individuals who

have donated blood with CJD, which would result in even more withdrawals with even more health impact. So I think my own view is that the blood issue, of course, is a very important one to discuss but, to me, dura mater is a different issue because we have a proven mechanism of transmission; we have a high dose tissue; and we have intracerebellar inoculation. So I agree there is an inconsistency here --

DR. WOLFE: Was there any discussion publicly of the blood issue or was it a decision not to do and there was no meeting on it? It was not discussed in Parliament; it was not discussed in the Ministry of Health, or what?

DR. WILL: I cannot comment on that level of discussion because I was not involved, but I am sure that there were major discussions in relation to CJD and, indeed, there was a meeting fairly recently at the Department of Health at which the issues of blood were discussed in detail, and which Dr. Ricketts and I both attended. So there have been major discussions about blood in the United Kingdom --

DR. WOLFE: And what happened there?

DR. WILL: Well, I think the current situation is that there has been no decision made to withdraw blood products at present. But I do know that today the Chief Medical Officer in the United Kingdom has made a press

release about the issue of nvCJD and the potential risk so the public are fully informed.

DR. WOLFE: Thank you.

DR. BROWN: Bob, did you have a comment that you wanted to add?

DR. ROHWER: No, just to second Larry's point that we are dealing with two different issues here. We have an existing disease which has been here for a long time. The new variant is a newly emerging disease.

There is another point, and that is that we have no idea where it is going to go epidemiologically. We have only seen 20-some cases so far but the projections are that we might see another 20 or 100 or we might see another 100,000. If it moves in the direction of 100,000, this would have a major impact on the total number of people bearing infectivity in their blood, and I think this would all have to be reconsidered in that light. We are not immediately at risk from this disease in the United States in any big way but it is definitely there, threatening Europe.

DR. BROWN: I think now perhaps is the time to ask the question I was going to ask before. One of the things that the Committee may want to consider, or undoubtedly will be considering is the possibility of relaxing some of the

worrisome exclusions with their recall consequences. I think one of the factors involved would be the impact that might have on the blood therapeutics supply and industry. If, for example, one were to say albumin really is not likely to pose any risk, why don't we just exclude albumin from consideration? If we did that, what would that gain in terms of supply and cost of the product to the industry and the American public?

I asked Peter Page, who spoke earlier, if he could come up with some at least rough figure to answer that question, and I would also address it to the Bayer people who are here, if they can give us just some feeling as to whether we are talking about, well, you know, that would improve things by 1% or whether it would improve things by 25%. Peter?

DR. PAGE: Using our most recent 6-months experience in which the financial effect was about $30 million, we would estimate that $4 million of that $30 million was attributable to albumin. Albumin gets out the door and infused relatively much more quickly than the other plasma derivatives. So on a proportional basis there is less of it left to bring back. That is only for Red Cross plasma, which is half of the recovered plasma and does not include source plasma.

DR. BROWN: Is there any information from Bayer, what your estimate would be?

MR. FOURNEL: It is a difficult question to answer. One issue that I think some of you are aware of is that there is a difference between the commercial fractionation industry and the Red Cross, primarily in that we use what is called source plasma. This is plasma that is derived from plasmapheresis donors. Usually it is about 800 ml/donation. That is the number I used on my slide. The Red Cross, because their plasma comes from whole blood donations primarily, uses as a source for plasma fractionation what is called recovered plasma, and it is usually in the range of 200 ml/donation. So they have approximately 4 times as many donors contributing the same volume as we would in the commercial industry.

For my company, Bayer, we make a product which is called Prolastin, an alpha-1 protease inhibitor, for the treatment of congenital emphysema. We are the only company in the United States that makes this product, and in order to supply a very urgent demand that exists in the United States, we have for several years secured plasma fraction from recovered plasma collected by the Red Cross in the manufacture of this product.

Regrettably, because of the high number of donors

involved and the statistics that you have heard about today, this product has been very severely affected for us, as was shown on the slide earlier. In fact, we estimate about 50% or more of our production has been affected by the current withdrawal requirement. So for Prolastin, for example --

DR. BROWN: The origin is Cohn fraction IV, is that correct?

MR. FOURNEL: That is right. So for Prolastin it would have an impact. For HSA for albumin we have been relatively unaffected, so to speak, because of our use of source plasma where the incidence so far of CJD donors has been lower. It is not zero now but it has been much lower for CJD-implicated donors.

But another issue that actually came up in our discussion that I want to point out is that albumin is used primarily -- or the primary concern I think for this group today is the use of albumin as an excipient in the biotechnology industry. For example, our recombinant Factor VIII product, Kogenate, currently has human serum albumin as an excipient. Because of the nature of the business, a very small number of lots, maybe only two or three lots of albumin at any given year will be set aside and used specifically as an excipient for an entire year's production of Kogenate. So if, by an unlucky chance, a CJD-implicated

donor was associated with a lot of albumin that was used as an excipient it would have a very big impact on our business, and I believe most of the other biotechnology industry.

So while I can't say that for us the immediate impact would be a significant revenue difference in terms of product that we would have to withdraw, I think the risk of withdrawal of biotechnology products under the current scenario is what is really the big fear for all of us.

DR. BROWN: Well, we are now at a point where we shall have a charge made to us by Dr. Murano, and he has one or two introductory comments before that. Dr. Murano?

Charge and Questions for the Committee

DR. MURANO: Good afternoon. Dr. Brown, Committee members, invited speakers, I thank you for your participation in this important forum and look forward to additional deliberations, guidance and recommendations.

Throughout the day we have taken a sojourn providing an abundance of information, spanning a variety of different but related topics. We were guided through the privileges, limitations and differences between guidances and regulations, and provided with an update of the rationale and conditions for our present policies regarding excipients and processing reagents.

We had a look at a realistic, if not a novel, approach to estimating risk in plasma derivatives. We had a detailed recap of the various memoranda issued, the range of affected products and quality of withdrawn products, and also a case scenario presentation, the transferrin case. We had an orientation focusing on operational aspects of compliance responsibilities impacting on recalls versus withdrawals. We were familiarized with a profile of the varied applications of defined plasma derivatives in the manufacture of therapeutics and of vaccines.

Dr. Wolff made us keenly aware of the delicate interplay of certain products and the exquisite sensitivity of manufacturing procedures with the slightest changes, and this is especially true for cell culture conditions.

We were familiarized with industry practices and the manufacture of biotech-derived and plasma-derived products, and the consequence that is associated with considerable economic burden associated with recalls, the last point of discussion.

We were familiarized with relevant animal studies, with relevant caveats, the results of which apparently were with odds with epidemiologic profiles from multiple sources.

Finally, we were presented with a profile on risk assessment characterizing the epidemiologic bad and good

news pertinent to CJD and the importance of public trust and involvement.

With this as a prologue, I would like to revisit the charge that we have already been introduced to by Dr. Asher this morning. I believe there are copies distributed. Then I would like to follow up with two specific questions.

(Slide)

I will read the charge: The TSE Advisory Committee has been asked to consider actions appropriate for the FDA to take concerning TSE-implicated secondary products, products in which before it was withdrawn a TSE-implicated plasma derivative or other TSE-implicated blood product was either added as an excipient or used as a reagent in the manufacturing process.

Several factors are currently considered and these factors were reviewed by Dr. Asher. I don't need to go through them again. Perhaps we could just put them up in skeleton form just to quickly refresh everyone's mind.

(Slide)

These reflected on the populations to be treated; the dose of the TSE agent potentially contaminating the secondary product in question; the manufacturing process, and the potential for eliminating the infectious agents; availability as a supply of the product; and the route of

administration.

(Slide)

Specifically to the questions, first of all, the condition and then the specific question. TSE-implicated plasma derivatives as excipients -- we will take them one at a time.

When an FDA-regulated plasma derivative has been withdrawn because a donor who contributed to the plasma pool was later diagnosed with CJD or was determined to be at increased risk of a TSE, FDA has recommended withdrawing other FDA-regulated injectable products containing the plasma derivative as an excipient.

Exceptions would be considered for life-sustaining and health-sustaining products in short supply for which no substitutes are readily available.

Specific questions are as follows: Do the members of the TSE Advisory Committee agree with this policy, and are there other criteria appropriate to consider in deciding whether to recommend withdrawal of products containing TSE-implicated excipients?

(Slide)

The second condition, question number two. This is for TSE-implicated plasma derivatives as manufacturing process reagents. Again, when an FDA-regulated plasma

derivative has been withdrawn because a donor who contributed to the plasma pool was later diagnosed with CJD or was determined to be at increased risk of a TSE, the safety of secondary FDA-regulated products manufactured by processes using the withdrawn plasma derivative as reagents is considered by reviewers on a case by case basis, and the factors considered in these deliberations are described in the charge which I presented a moment ago.

The question to the Committee is as follows: Do the members of the Committee agree with this policy, and please comment on the value of the factors currently considered by FDA in case by case decisions about secondary products prepared using CJD-implicated plasma derivatives and, indeed, suggest -- we would appreciate additional suggestions on any other factors that FDA might consider appropriate.

I was instructed to be mercifully brief and I was. I hope I fulfilled those criteria.

DR. BROWN: Thank you very much. That concludes the Committee's education. We are now asked to address specifically these two questions, but you notice that they have left us a little moving room. You will also notice that we are in the ironic position of judging -- not judging but being asked to give advice about secondary products

which, of course, will be determined by our opinion on primary products for which we are not asked to render judgment. Therefore, implicit in everything we say on secondary there will be a judgment rendered on the primary, but that is not our specific charge today.

Let's just see where the discussion goes by just opening it carte blanche and following it for a little while. Ray?

DR. ROOS: I just want to make one comment which perhaps bypasses these questions in a way but maybe it is important. That is, the last speaker told us about how really there is some jeopardy involved in the situation at the moment in the sense that there are small lots of albumin that might determine the availability of AHG, and if there is a Creutzfeldt-Jakob case that is identified a lot could be discontinued and there would be a large impact.

One wonders, in a way similar to the growth hormone situation, whether the real solution to that isn't recombinant products and at least it seems to me to be prudent and reasonable for us to encourage the use, whatever that word "encourage" means, with respect to AHG, as well as albumin, as well as these other blood source products that either have recombinant products available or could be made available. Then perhaps some of these questions become

moot.

I realize that isn't the situation at present, but I thought it important at least to bring that out because maybe that is the best solution and the best answer to any of these questions.

DR. BROWN: Alternatives, right.

DR. ROOS: Some of them exist.

DR. BROWN: Yes. I was going to say yesterday we were really dealing point blank with risk-benefit. Today we are dealing more with risk rather than benefit. The benefit is demonstrable. Where there are alternative solutions and preparations, I think the blood industry itself is very much behind them. Obviously, recombinant anti-hemophilic factor has taken off, and my guess is, like growth hormone, it will in the near future replace cryoprecipitate as a source for anti-hemophilic factor. But there are others which are not likely, I think, to be cracked in the near future. Albumin I doubt -- well, it is not for me to say but there are certainly difficulties that are greater than that for anti-hemophilic factor in terms of recombinant technology. I think everybody on the Committee would agree, not just form the point of view of CJD but from the point of view of any blood-borne pathogen, that fully adequate substitute recombinant products are to be and will undoubtedly be used.

Does anybody disagree with that?

MR. FAITEK: Doctor, I realize it is not in the purview of this Committee to endorse what you just said but could we anyway?

DR. BROWN: Sure. As the Chairman, I allow you to do that.

(Laughter)

MR. FAITEK: One of the most disappointing problems in the hemophilia community has been the lack of the recombinant factor taking over the greatest supply of factor for hemophilia. Obviously, one of the reasons that we are is the hemophilia HIV catastrophe, and that is a good part of what is driving this meeting. I think that as far as blood product safety is concerned for hemophilia, the ultimate solution is obviously recombinant factors because these pathogens are going to be coming down the line one after another ad infinitum. So I would endorse the Chairman's comments regarding the eventual use, and over a shorter period of time of recombinant factors for the treatment of hemophilia.

DR. BROWN: Okay, I think that is transcribed and in the record. yes?

DR. WOLFE: I think I generally agree with this policy. There is a red flag in here, which is that

exceptions should be considered, which I think they should be, for life-sustaining or health-sustaining products in short supply for which no substitutes are readily available.

I will tell you a quick story since you gave us a story. My transition back 26 years ago from NIH, where I was happily working, to starting the group I did was occasioned by a company claiming that there was a short supply of intravenous fluids. It was Abbott Laboratories who were then supplying half the intravenous fluids in the country, and it turned out that due to some change in manufacturing there was a contamination in Abbott fluids. They convinced the Centers for Disease Control and the FDA that were there to be a recall, which there was -- there should have been and ultimately was of these products, the nation would be in a crisis because of not having adequate supplies of intravenous products. I called the other manufacturers and it was easily determined that no such crisis would occur.

More recently, in the context of our discussion in April this year concerning gelatin, some of the producers of gelatin in Europe tried to convince the FDA and their committee that there would be a crisis if there wasn't a continued allowance of gelatin.

So I think that there needs to be some

verification by the FDA, independent of the claims made by companies that are in some cases accurate but in some cases may be self-serving to avoid the losses, whatever they are and, you know, making it appear as if there is no other way people with hemophilia, or whatever else disease, can do it.

So I think that if we are going to allow exceptions, which I think we should and have to, there needs to be verification for the short supply for which no substitutes are readily available.

DR. BROWN: Carried out by the FDA?

DR. WOLFE: Yes, the FDA. You know, FDA goes into these companies for other purposes to look at good manufacturing practices. I think it is just a matter of getting some written documentation of what the supply is relative to the demand that this is short and, therefore, it occasions an exception.

DR. BROWN: Well, naive as I am, I had always assumed that the FDA would be taken proper care to do this. Can I ask the FDA if this is part of their usual procedure when a shortage is claimed?

MR. DUBINSKY: Mike Dubinsky, with the Office of Compliance. We do take the step of determine as best we can what the supply is. We do have some internal information, Through out adverse experience reporting rule, there is a

requirement that the manufacturers at least apprise us of distribution numbers of products. So we do have a fell for what is out in the market, Even though that type of information is not available to the public, it is available to us. So we do make those types of inquiries to verify claimed shortages.

DR. BROWN: So, I guess, for the record we can say that there has been concern expressed that the FDA take some pains to verify a claim made by an interested party. Jay?

DR. EPSTEIN: I would support that statement, however, I would add that these determinations are very difficult and that they come with a very high degree of uncertainty. We, of course, have had a lot of experience trying to do this in the face of the CJD risk-related withdrawals and we have been faced with situations in which we have been told that major suppliers have no inventory, or that half of all inventory is impacted, or that all product made for the next four to six months will be impacted. Routinely, we do not know how much of the product which is on the market has already been consumed. We can learn easily what percent of lots on the market are affected but we don't necessarily know what part of supply that is either for that particular manufacturer, let alone for the entire nation's supply.

There are also kinetic factors that are close to impossible to work out, such as how much inventory is distributed, how much is in hospitals how much is in major warehouses, how much is in the pipeline that could quickly be released etc. We have found that one of the impacts of a consistent withdrawal policy is never knowing how close to the brink we push the system in terms of the availability of these needed products. So the answer is we always try and the answer is we don't generally know.

DR. SCHONBERGER: While Jay is up there, I would like to commend Jay publicly because I have watched him at work on this very issue and, quite frankly, I think the current policy has led us to the brink several times and the only reason that we haven't really had a major crisis in the country is because of Jay's personal involvement in trying to settle these issues.

I can tell you that the policy in 1995, I believe, included a provision that if a shortage were to occur, the companies should bring that shortage to the attention of FDA and they would be given permission to reissue the products that had been affected by the withdrawal or the recall. However, that safety valve to the shortage issue has been found not to work. The reason for that is more legal than anything else, as well as just the difficulties in taking

product, bringing it back to the company and then sending it back out again and having the same assurance that it meets all the qualifications, and also that the companies are not taking an unusual liability for doing that. At least, that is my understanding of why that particular safety valve is no longer here.

So the country right now is working on a policy that doesn't have built within in a safety valve for potential shortages created by this CJD concern. The one safety valve that really does exist is Jay, and he has been doing an excellent job in trying to do that but I am very much worried about how long he can balance this situation and keep us from getting into that type of shortage problem.

DR. BROWN: Are there other -- yes, Ray?

DR. ROOS: Another question. I guess there were two parts to this first question --

DR. BROWN: Yes, I think we are going to consider the first question mark in and of itself. Then we are going to consider the second.

DR. ROOS: Well, above the question mark there were two sentences, and the second one is exceptions would be considered for life-sustaining or health-sustaining products in short supply for which no substitutes are readily available. I just wanted to throw this out for the

moment, let's say an exception is made, what are the chances that this product would be used or that the company would go ahead, if an exception was made, and use this product? In other words, from what I heard from Dr. Asher originally, recommendations were made by the FDA and I just bring up for discussion here, you know, even if we make an exception does that mean that the company, in fact, will distribute this product in a continuing basis? Or have we essentially stigmatized this product --

DR. BROWN: What do you mean by a continuing basis?

DR. ROOS: In other words, have we given a stigma so that the reliability issues are going to override okaying this product for some exceptional use.

DR. BROWN: In other words, you are saying if an exception was made for --

DR. ROOS: Anti-hemophilia globulin, that the company still might hesitate to use and distribute that anti-hemophilia globulin.

DR. BROWN: It just doesn't seem to me that a company wouldn't ask to do so if they didn't have in mind doing it.

DR. ROOS: Well, I am not sure they are asking to do it. I think the FDA is reviewing and saying a

Creutzfeldt-Jakob case was discovered as the source of this albumin. The recommendations here are that we withdraw this product but because it is important you are allowed to distribute it.

DR. BROWN: So you are saying an FDA-generated exception without a request for that exception to be made from the supplier company?

DR. ROOS: I am concerned that there is a stigma on this product and that even if at that point you say oh, this is an exception because it is so important -- I am concerned that the product is still stigmatized here and that there is going to be reluctance for distribution of the product.

DR. WHITE: I think that is what Larry was saying when he said legal. The problem with that is that the product has been declared unfit --

DR. BROWN: Tainted.

DR. WHITE: -- for use at one point in time, and then is released for use not because anything in the product has changed, and I do believe the companies would be concerned about using that product for fear of legal repercussions.

DR. ROOS: I am not saying that we shouldn't act on this question as we see fit; I am just saying that we

should be aware that by releasing this product and saying it can be used, it doesn't necessarily mean we are going to rescue it and bring it back to the public. That is all. Maybe there are other ways to carry out what we want to do short of this.

DR. BROWN: Well, it also opens up the whole discussion, which I don't think is probably our business to talk about, of informed consent, of product labeling. Are you going to put, you know, a red star on every vial and then from that point on it is like The Scarlet Letter. That is what you are talking about. Yes?

DR. LESSIN: There is another factor in this equation which we have discussed in previous meetings of this Committee, and that is pool size. I think there was a recommendation, or at least it came as part of a discussion back in '96 that by reducing pool size the impact on total supply at the time of withdrawal would be lessened. Has industry done anything in that regard? I don't think so but I would be willing to hear more about it.

DR. BROWN: Industry can talk about that. It was a subject addressed by a congressional subcommittee towards the end of July, and pool size was specifically under discussion. My sense at that meeting was that at that moment, no, pool size at the end of July was not

substantially different than it had been a year, two years or five years before. My sense also was that it may be different very soon. I think the congressional committee probably wound up taking a somewhat dim view of very large pool sizes, mainly because of this common sense problem of having phenomenal recall difficulties with huge pool sizes. But I don't know, maybe someone in the audience can tell me whether the committee has itself issued any kind of statement about this. Does anybody know what the subcommittee has done about this, if anything, yet?

DR. WOLFE: We did make a recommendation though at that meeting, that Dr. Lessin is referring to, to the industry to reduce pool size, and it has been a year.

DR. BROWN: I am talking about just three months ago.

DR. WOLFE: You are talking about the congressional committee --

DR. BROWN: Yes.

DR. WOLFE: -- I am talking about this Committee that made that recommendation.

MR. FAITEK: A couple of comments, one of the things that Dr. Roos brought up and that I want to extrapolate a little on is that giving exceptions might eventually perpetuate product shortages. If the companies

can get an exemption because of shortages, it might perpetuate shortages.

The other thing is that reduced pool size would not only impact withdrawal but also reduce the possible impact of infected product on the population.

DR. BROWN: Yes, that is a subject that I have been much interested in myself over the past several months. It is one that I think is a little bit more complicated than it seems. What you suggested is not necessarily so. It may be, but it may not be, and there are lots of reasons for that but that is a whole other hour. In any case, we can all agree that small pool sizes certainly minimize the problem of product recall. That is certain. Yes?

MR. BABLAK: My name is Jason Bablak. I am with the National Plasma Products Industry Association. I just wanted to address the pool size question. It was brought up at the hearing as you all said. The industry voluntarily agreed to limit the pool sizes at the maximum of 60,000 donors, and we believe that this will have a very limited impact on recalls due to the repeat donations.

DR. BROWN: Limited?

MR. BABLAK: Limited.

DR. BROWN: Impact on?

MR. BABLAK: On recall situations due to the

repeat of plasma donors.

DR. BROWN: For plasmapheresis?

MR. BABLAK: Correct.

DR. BROWN: But not for voluntary whole blood donations.

MR. BABLAK: Right, it will have no effect on that.

DR. WOLFE: Have other parts of the blood industry made similar promises, or whatever, to limit pool size?

MR. BABLAK: At the hearing the American Red Cross also said they were working on limiting their pool size to 60,000 as well.

DR. BROWN: There was also, as I recall, floating in the air the idea that it would not be a bad idea to set aside from a given pool a certain amount of albumin to be used as a stabilizer and an excipient for that pool. So there would be no cross-contamination possible between pools.

MR. BABLAK: I think that was mentioned as a theoretical possibility but due to the manufacturing process that may not be possible.

DR. BROWN: I think the Red Cross is already doing it. Am I wrong?

DR. PAGE: Peter Page, with Red Cross. I should

clarify that in the United States the Red Cross does not fractionate itself. We have a contract with one of the commercial fractionators to process our plasma for us and return finished product to us for distribution. So the licensure of the derivative product from our plasma is really the fractionator, not the American Red Cross itself.

DR. BROWN: But is it accurate to say that that fractionator has now under consideration, or has already begun to use albumin from the same general pool for use in that pool?

DR. PAGE: I am not part of those discussions but I do know that American Red Cross has requested of that fractionator that that be done. I can't speak to the status to the response of that request.

DR. BROWN: Comments? Questions? Discussion? We could, if you would like, poll on the first question, the first part of the first question, which is do the members of the TSE Advisory Committee agree with this policy? We can then focus our discussion on the second part of it, which will give us an opportunity to qualify the first part, should we wish to.

DR. SCHONBERGER: Why not?

DR. BROWN: All right. We are voting on our answer to the first question, do the members of this

Committee agree with the policy as it is stated in TSE-implicated plasma derivatives as excipients? Linda?

DR. DETWILER: I do not, and I would like to explain that. I do not because I think for a person that is later diagnosed with CJD, even though I don't see a scientific reason to do that, there is this perception, or even I have a hard time with saying, ah, that is the best thing to do. But if I take science into account I wouldn't even do that. Then the increased risk, to me, we are protecting potential risk from a theoretical risk and, to me, that just goes too far.

DR. BROWN: Ray?

DR. ROOS: I was involved in some early discussions regarding our blood derivatives in general and recall withdrawing those and how it should be accomplished. I thought that I was concerned about biologicals being in short supply, and it seemed to me in those instances that if there were unusual circumstances the products should be appropriately labeled with the proper caveats, and that the physician and the patient should be given the opportunity to use it if they needed to, and there are clear situations, you know, if you had somebody who was 95 years old and needed some plasma-derived product I would be less concerned about this person using a product that might be from and

adverse Creutzfeldt-Jakob case.

As it was, I think a decision was made for those plasma derivatives, guided to a great extent by assuring safeguards of blood products in the United States, and I think that that was an appropriate decision given those pressures. However, I am still stuck with that idea in my mind and in this case, with the secondary products using these excipients, I think that there should be some exceptions to the rule, and I guess that is what we are talking about here, these exceptions.

DR. BROWN: We will be.

DR. ROOS: Right. I think that in a way it is a little bit inconsistent because in the case of the primary product if there is a plasma derivative we are not going to allow its use under any situation, and here we have a secondary product in which that same plasma derivative exists but now as an excipient in which we have a different guideline. So it is that inconsistency that is a bit of an issue here, and it makes me concerned that this is going to be understood by the public and also that it is going to have an impact on the distributor of the product itself, which is what I raised. That is, what really will be the impact of this from the manufacturing point of view? Are they going to be guided if we think that there should be an

exception? So I am concerned about the inconsistency about whether it is really going to have an impact. Nevertheless, I think with proper guidelines the exceptions seem to be me appropriate. So I think I agree with the policy, although I think it is important to build in the proper guidelines.

I also want to reiterate that I think that if we have recombinants for some of these and appropriate encouragement for the use of those recombinants, then we wouldn't be kind of struggling with this difficult issue. So that is a long yes.

DR. BROWN: Yes, that is the longest, most complicated yes I think I have heard.

Before we continue and we will give a chance to Ray and Linda to revise their opinions if they so choose, depending on the answer to this question, I would like to ask if any excipients derived from Cohn fractions I and II, that is to say the cryoprecipitate and fraction I, II, III, are there any products made from either one of those two Cohn fractions that are used as excipients? Anybody have the answer? My guess is no.

DR. EPSTEIN: Immune globulin is used as a diluent for specific immune globulin, for example.

DR. BROWN: Okay.

DR. EPSTEIN: So if you have anti-rabies or

anti-tetanus you may, in fact, formulate it by dilution into immune globulin. Technically speaking, that is used as an excipient. And we have encountered that kind of situation.

DR. BROWN: You have?

DR. EPSTEIN: Yes, we have.

DR. BROWN: So like immune globulin from pool X could be used as an excipient for specific anti-rabies globulin made from pool Y. That would be a possibility.

DR. EPSTEIN: Right. I am not saying that specific case has occurred but that kind of scenario has occurred.

DR. BROWN: Are there any other products from either one of these first two cuts of plasma processing that are used ever as excipients for anything?

DR. EPSTEIN: I don't know of another. Certainly, most of the excipients will be albumin.

DR. BROWN: Right.

DR. EPSTEIN: Or PPF.

DR. WHITE: Well, cryoprecipitate has fibronectin, fibrinogen, von Willebrand factor. Is fibronectin used as a stabilizer or excipient in any product that you are aware of?

DR. EPSTEIN: Not to my knowledge. Now, it is a component of fibrin sealant, which is not an intravenous use

product; it is a topical product, not yet recognized under licensed but there are applications. We do know that cryoprecipitate or fibrinogen products will be components of a complex product which results in fibrin sealant. Now, fibrin sealants can be applied within a body cavity and they can be directly applied on the brain or a coronary artery or wound and we are, therefore, likely to encounter situations in which fibrinogen made as a pooled product could be subject of withdrawal over CJD risk. That has not yet happened but that would be another possible scenario of a cryo fraction.

DR. BROWN: Thank you. Presumably that doesn't change either one of your opinions. Gil?

DR. WHITE: Well, for a guy who has been educated all day, I feel more confused than ever on this topic. When we last visited this I guess we didn't have a lot of epidemiological data and we had some experimental data that said that these agents were probably not transmitted by blood. Now we have a relative lot of epidemiological data which says it isn't transmitted, but we now have some experimental data that says it is. So I am kind of left in the middle and don't feel like we have necessarily progressed a whole lot from where we were the last time we visited it.

Based on that, I think I would agree with continuing the current policy until we have a little more information. So I would agree with the current policy based on that, although it is not my opinion that albumin is likely to transmit prion-mediated disorders.

DR. BROWN: Barbara?

MS. HARRELL: I agree that the current policy should stay in effect. With a lot of statements being made today about we have very little data, repeated time and time again, I feel they are very uncomfortable with taking any risk at all with the blood supply. I also like Canada's conservative philosophy because they think it very important for the public to have confidence in the blood supply. Also I consider the public witnesses today, the lady whose husband died, and her concerns, and since that is the group that I represent I do agree that the policy should remain as it is.

DR. BROWN: Ed?

DR. TRAMONT: I disagree. I think Linda summarized my thoughts quite well.

DR. BROWN: Leon?

MR. FAITEK: Yes.

DR. BROWN: Sidney?

DR. WOLFE: Yes, I just want to clarify a point

though because the first sentence here says that FDA has been doing this, and the way the exception sentence is worded it isn't clear whether FDA in the past has made exceptions. Can we just get an answer to that?

DR. BROWN: Yes, the transferrin case that was presented this morning is such a case.

DR. WOLFE: So that is the one exception?

DR. BROWN: I don't know.

DR. WOLFE: So current FDA policy is to recall but to make exceptions. I would support --

DR. ASHER: We would entertain exceptions if such a thing happened, but it has not to my knowledge been requested.

DR. WOLFE: Okay. So I vote yes.

DR. ASHER: Transferrin is not an excipient. We are talking now about excipients.

DR. WOLFE: So there haven't been any --

DR. ASHER: Not for excipients.

DR. WOLFE: But there haven't been any requests either.

DR. ASHER: No.

DR. WOLFE: So the occasion hasn't arisen at all.

DR. ASHER: An occasion has not arisen.

DR. WOLFE: Okay.

DR. BROWN: I will vote yes.

DR. LESSIN: Considering my vote, one of the areas that we haven't visited today, and I doubt is the purview of this Committee because I think we were told yesterday the FDA doesn't regulate doctors; it regulates products, that is, the provider utilization of these products. I mean, we know from our experience in blood banking that utilization guidelines and that area have changed rapidly in the past few years. The threshold of hematocrit for transfusion, the threshold of platelets for transfusion, all of these things have changed. I think provider education has been quite lacking in this area.

My experience with the shortage of IGIV a couple of years ago when there was a big withdrawal was that, yes, the product was somewhat hard to obtain. I had about six patients on it at the time. Instead of treating them every three weeks I lengthened the interval to every four weeks. The other companies were able to fill in the gap, where one company was short just exactly the same story that you mentioned earlier. In fact, there was no real effect of shortage. I am sure there are exceptions to those exceptions but at present, with those caveats in mind, I will vote in the affirmative.

DR. BROWN: All right.

DR. SCHONBERGER: I would like to put my vote into a little bit of context. I would like to indicate that I was impressed with Dr. Rohwer's assessment of the efficacy of the current policy, which he indicated would be hardly measurable. I was impressed with Peter Page's description of costs, over $100 million so far for the Red Cross and mounting. I was also impressed with my own experience and what I know is Jay Epstein's struggle, which is the constant risk of creating shortages. Although the surveillance for such shortages is not very clear, you have the sense of backlogs on order and disruption of the system that cannot help but cause people to not get a product that they need or would benefit from. I am also impressed from the epidemiology we have heard that there is no measurable benefit to this policy in terms of a reduction in cases of Creutzfeldt-Jakob disease. I am also impressed that people are talking about trust and getting a sense of security about the blood supply but ultimately, if we believe what we heard today, the policy gives a false sense of security. And some day in retrospect, people will look at that and all these committees are participating and telling the public that they are getting protection that they are really not.

That part of the issue that you are now raising about education of the public, that in this situation there

may be a low level risk -- I am not saying that it never happens. We have heard the epidemiology and its limitations and so on, that there may be a rare case that could be transmitted by the blood supply but, clearly, it is a low level risk and it is certainly not clear that what we are doing as part of this policy is really significantly lowering that risk.

Finally, we have heard today some actual negative consequences of this policy. We heard somebody talk about the extreme concern about some of the public that wasn't going to get rabies immune globulin when I think most physicians would have said that that was a no-brainer to decide what that person should have gotten.

Then I have personal experiences of getting people calling me as a result of this policy who are quite frightened because they have received a message that the product that they had received had come from a CJD donor, as if the product they received was a whole lot different form other products that they have received in the past. Some of the hemophilia patients that might call, you know, are not aware that they have already been exposed. We heard that statistically.

Then there is the issue of abusing a public health measure, which is recalls and withdrawals, for something

that has no measurable benefit and there is the problem of cynicism and calling "wolf, wolf" too much and I would suspect that the enthusiasm for going after these recalls over time is going to get lower. Now, I don't have the data to absolutely support that but I do have some personal conversations with people that suggest that this "wolf, wolf" phenomenon may be occurring with this particular issue.

Nevertheless, I understand from what was said before that a lot of this policy and this problem stems from mistakes made in the past with regard to the AIDS epidemic. I was personally involved with the AIDS epidemic and was involved in making the decision that blood was, indeed, transmitting disease to patients. We did an analysis on that, and I do feel, and I do agree that we were slow in our response. That is, the government was slow in its response to that issue. But I don't want our slowness in response to that issue to create a second mistake now by overreacting to a theoretical risk without it having an easy kind of solution to reduce that risk.

But given the question that was asked in the context of the specific question, my vote will be yes.

(Laughter)

DR. BROWN: You are now in second place, Ray.

(Laughter)

DR. HUESTON: I am still reeling from that analysis and response.

DR. LESSIN: Don't let it affect your vote!

(Laughter)

DR. HUESTON: No, it won't affect my vote. I am impressed that we do, in fact, have a number of risk management strategies available and at times I get frustrated that here we all are and, in fact, we make policy decisions daily in the absence of complete information. Nevertheless, with the information we have available we can manage and reduce risk, and I feel that this blanket response of withdrawing the situations in which TSE-implicated plasma derivatives are used as excipients is too broad because I believe that we do have opportunities to reduce that risk. We talked about a number of them -- pool size, the age of the donors, the route of administration and the dose.

My concern is once one goes down this path for any length of time, then one is faced with the challenge of proving things of safe. So having established a policy of withdrawal, how does one then turn around and document that something is safe when, in fact, a scientific method does not allow us to prove safety? So, in this case, I vote no.

I disagree with the policy that is currently used.

DR. BROWN: The tally is 8 agreements and 3 disagreements.

Now, we have the second question, are there other criteria appropriate to consider in deciding whether to recommend withdrawal of products containing TSE-implicated excipients?

I am going to throw on the table an exception that will gut the first answer. I am going to suggest for the panel's consideration that they except albumin from withdrawal policy. I do this because, one, even primary products epidemiologically have not been identified as causing CJD.

Two, the two experiments that do bear specifically on the problem, with all of the qualifications that apply to experimental data translated to humans, nevertheless, those two experiments indicate that of all of the products involved in blood therapeutics albumin is the least likely to be infectious even as a primary, let alone an excipient.

Third, because the production of albumin from the Cohn fraction from which it is derived involves two further steps that could further reduce infectivity. They haven't been studied yet but there is no reason to suppose they wouldn't have some effect, and they are further

precipitation and filtration steps.

My judgment about albumin is that it is so close to being zero risk and it is such an important element as an excipient that I would propose a blanket exception for albumin. I throw that open to the Committee for discussion. Ray?

DR. ROOS: So, Paul, if we go along with that, there remains an FDA guideline in which if albumin is used as a primary product rather than as an excipient, it is going to be disallowed. Is that correct?

DR. BROWN: We are not going to deal with it as a primary, and my feeling about it as a primary might be a little different, but excipients, no.

DR. ROOS: Why?

DR. BROWN: Because the amount, just the amount. I mean, if you are going to give somebody a unit of albumin as a plasma expander, for example, I don't know what the volumes would be but the amount of albumin as an excipient would be logs lower. It would basically be that. That is why I wanted especially to know about any products form Cohn fractions, the cryoprecipitate and I, II, III, and had the answer been no, there are no excipients that are derived from those, I would have voted against it. But I think we have evidence that I, II, III has to be worried about a

little bit, and I don't know if it has to be worried about as an excipient. I think it certainly has to be worried a little bit about as a primary and there is just not enough information to know about, but albumin I feel very comfortable about. Bob?

DR. ROHWER: As your co-collaborator, I feel more comfortable about albumin than any of the other plasma derivatives we looked at, but I do want to put this out on the table just so that people know precisely what the limits are to the interpretation of those experiments.

In the mouse-adapted CJD experiment we inoculated 88 mice with albumin. None of them got sick. But if you look at how much albumin we actually inoculated, what you can take home from that is that the infectivity associated with those inoculations was less than 1 unit of infectivity per 3.7 ml of 10% albumin. That is what it would have worked out to.

To do it on a grander scale would require tens of thousands of animals. It is a limitation of this type of approach. Therefore, we did the spiking experiment. In the case of the spiking experiment, we removed 4.8 or 7 logs of infectivity during plasma fractionation from the albumin fraction. However, if the blood had been infected at the rate of 10 infectious units/ml that works out to about 1

infectious unit per 10 liters of 10% albumin.

So you have to keep in mind that you can attach some numbers to this, and it is not that it is zero, it is that the relative risk is vastly smaller than it is for any other component. Tying that in with the epidemiology and everything else, you should take that into consideration.

DR. BROWN: Also, it is important to know the negative, and here we are talking negatives, not positives. The negative came about after intracerebral inoculation. God knows where it would have been after intravenous inoculation. We already know that is probably 100- to 1000-fold less efficient. I think there is just too much going against albumin as a danger to warrant recalls and worries about it. That is my opinion and those are the reasons. Yes, David?

DR. ASHER: In general I would agree with everything I have heard. I do want to point out that albumin is used as an excipient in the preparation of measles, mumps, rubella vaccine. Every child in America is immunized with this vaccine as a condition for going to school. I am not sure that the recommendation to exempt albumin would meet with public approval if it were known that measles, mumps and rubella vaccine contained a withdrawn albumin.

DR. BROWN: Yes, I think that is a good point. I sort of expected you to make it. Two things, I don't think it is the purview of this Committee to predict and base our advice on what we think the public would or would not accept. That is your problem.

(Laughter)

Second, I see no reason --

DR. ASHER: I think it is all our problem.

DR. BROWN: It is your specific policy problem. We are not making the policy. But I see no reason, for example, if there was agreement about that, not to exempt vaccines. You know, we can tailor advice any way we choose. If we exempted albumin for products that were not vaccines, that might be a more acceptable solution. Certainly, it is a practical one. Yes?

DR. WHITE: I guess from the microcosm of hemophilia treatment, I would disagree with that proposal to exempt albumin, and I would do it only from the point of view of recombinant Factor VIII. Having albumin as a stabilizer for plasma-derived Factor VIII I don't think adds anything to the risk that is already inherent in plasma-derived Factor VIII. But using albumin as a stabilizer in recombinant Factor VIII takes a product which has absolutely no risk of blood-borne disorders to a product

that has possibly a finite risk of a blood-borne disorder. And I just don't see that that gets us where we are trying to go.

I am very keenly aware of the possibility that contamination -- contamination is the wrong word, but of a donor with CJD in a lot of albumin which is used in the formulation of recombinant Factor VIII could lead to quarantining and recalling of as much as 60% to 70% of the Factor VIII supply that is currently available, which is an enormous reduction in the amount of Factor VIII that is available and could well cause some serious supply problems. Despite that, I still would be concerned about exempting albumin at this point in time.

DR. BROWN: Yes, I think that is a good point. If we were going to say we will exempt albumin, we have two possible exceptions to that exception now before us. One is vaccine and the other is recombinant products, or shall we say any non-plasma-based product? As you say, then you are adding something to nothing. Linda?

Incidentally, I through this out. The question was are there other criteria that are appropriate? I am suggesting one. We have got that modified a little bit now. But if other people want to discuss other things than this, at any time feel free.

DR. DETWILER: I guess I am getting more and more uncomfortable here that I guess the majority of the Committee does feel that there is potential risk. Yet, we sit here and we know that what would be taken out may only be the tip of the iceberg. Is that really being responsible? I mean, if there are unreported cases going into the blood supply; if there are incubating cases -- I mean yesterday we sat and we said dura mater is okay, but you could get dura mater from an incubating CJD patient. Right? But, yet, we said it is okay and there is no way to screen that out right now. We can't screen out. And I am uncomfortable. Are we doing this just because there is no other way out of it, that there is no way to screen the population and this is the only way to go? So it is a "feel good." We are making the public feel like we are doing something.

If we are going to do that, if we think there is a risk or the Committee thinks that, go to the other extreme and just put a warning that everybody is under a risk. Because you are going to go one way or the other. I don't know how you can get out and just say, well, all that other stuff is okay, or lead the public to believe it is okay.

DR. TRAMONT: Linda is talking about trust. Basically, the best way to get trust is to tell the truth.

Maybe we ought to say we don't know. That would be the best thing to do.

DR. WHITE: Well, I am not saying you shouldn't put a warning on there anyway. I mean, there should be a warning on there. I mean, anybody who takes red blood cells or any blood product at all is taking a risk, and they should know that. And most people who take them don't know that. I mean, nobody who gets a red blood cell ever gets the same kind of warning that a patient with hemophilia gets when they start on Factor VIII for the first time. So do both.

DR. BROWN: Yes, this opens what I have always thought was the major issue. I am not terribly worried about the crying wolf too often. That really doesn't impress me at all because if it is made part of an ongoing, deliberate effort to educate the public to the best estimates we have about risk, then the wolf is no longer a wolf; he is a very accurately perceived sheep. And people will begin slowly to understand the risks inherent in the transfer of tissues, and as we get more accurate information, I entirely agree, our obligation is to keep the public up to speed on what we know and let the public be educated and ultimately come to the same kinds of decisions that we would so that we no longer become the public's

caretakers. But this is a very slow process and I think we are only beginning to do it.

There is also the question of risk takers, which was wonderfully illustrated in Canada and which Maura Ricketts could tell us more about, but basically risk is not a bell-shaped curve in the population. Oddly enough, it is a bimodal curve and there are risk takers and non-risk takers, and there is not a whole lot in between the two. So that is a fact of life as well. But let's get on with any other discussions that we might have before we have a look at the second question.

DR. LESSIN: In terms of other criteria, this was addressed in one of the guidances I think or one of the memos from FDA, that is, the recipient and the exceptions could include situations where the recipient has a short life expectancy, or is unlikely to outlive the latent period or the incubation period for development of CJD.

DR. BROWN: Would this in any way be covered by life-sustaining or health-sustaining products? I agree, this was one of the factors that was put up on the board for us to consider but it doesn't appear in number one as a criterion for an exception. For example, for the treatment of a fatal disease?

DR. LESSIN: Yes, short life expectancy.

DR. BROWN: Right, a short life expectancy disease.

DR. LESSIN: Maintaining quality of life for that individual is of importance.

DR. BROWN: Is there discussion on that as a criterion for operating or driving or inciting the FDA to make an exception?

DR. ROOS: I am not sure how it would work. That is the only thing. I mean, you are talking about a product withdrawal and if a product is withdrawn you can't use it for somebody who has a short life span.

DR. BROWN: No, I thought the idea was that you could use a dangerous product, such as this might be, in a patient who has an illness that would be fatal within a short period of time. That is the way I understood it, a short duration illness.

DR. WOLFE: But the unit of analysis there is the patient and the lot decision has been made by the FDA that you are not going to put yourself logically in a position where that patient will have that choice. I guess that is the only problem.

DR. BROWN: How would you deal with this, Jay? Any ideas? Both of these are correct? I mean, we are talking about the possibility of an illness, a short

duration illness but it is true that is the patient and not the lot.

DR. EPSTEIN: Yes, I think that Syd captured it correctly, that the decision the FDA has to make is release of the product or withdrawal of the product, and products have many indications. Certainly, the FDA would entertain distribution of a labeled product, and we have no problem with the idea that it could be used in appropriate medical settings. But, as has been said earlier by Dr. Schonberger, there has been resistance by the industry to distribute any specifically labeled product. No manufacturer has stood up and said that they would distribute a product that was known to be implicated and label it as such. That is where the strategy bogs down.

DR. BROWN: Their preference would be to kill the product altogether rather than to red flag it.

DR. EPSTEIN: I think we should let industry represents speak for themselves --

DR. BROWN: Yes.

DR. EPSTEIN: -- but that has been the pattern to date.

DR. BROWN: Bayer?

MR. FOURNEL: I am really not qualified to answer that question.

DR. WOLFE: Just answer it for Pharma then, not for Bayer.

(Laughter)

MR. FOURNEL: I think you can all understand the legal issues involved. If we were to redistribute a product that has knowingly been withdrawn for reasons that this Committee and other august bodies have decided represents an increased risk, there is a serious liability issue involved. So we need some way to resolve that issue I think.

DR. BROWN: Would there be even if the FDA gave you the green light? That is to say, because the FDA has said okay you would still run a legal liability as the distributor?

MR. FOURNEL: Again, I am really not the one to ask the question.

DR. BROWN: Any lawyers in the room?

MR. FOURNEL: Yes, that is what we need.

DR. WHITE: I can answer that. Yes. It doesn't take a lawyer to answer that.

MR. SIEGEL: This is Jay Siegel, Office of Therapeutics. That particular criteria, which is number one on the list of six we gave regarding question number two, is one that we can and have used in assessing in the area of products used in further manufacture, particularly in

experimental products. We have had cases with an experimental product for CMV retinitis, and another experimental product for a uniformly fatal congenital disease in which, for that reason and others, we have not stopped the studies.

There are a number of differences, of course, there. One is that under protocol you know that it is being restricted only to that particular population. A second important one is that the populations in both cases the patients, or in the other case the parents, were fully informed of what was known about the potential risks of transmission of a TSE.

DR. BROWN: All right, Ray?

DR. ROOS: So, in a way, this gets back to an issue that I wanted to raise in the beginning, and that is we kind of kid ourselves I think perhaps by that second sentence with the exception, and we probably would like to see it occur but it may not in reality. In other words, once that product is withdrawn it may not come back, and I am not sure of an easy way around that.

DR. BROWN: Well, apparently we are not going to be able to solve that today because Jay has told us that that is a factor and a criterion that would be used to consider exceptions, but we don't have any industry input to

know whether that would be agreeable. So it perhaps is best to move off that topic and onto something that perhaps we can agree on. Are there any other criteria that you think would be appropriate for the FDA to consider in their withdrawal policy? Leon?

MR. FAITEK: I would just like to mention that factor products are already implicated in transmission, for example, of parvovirus. So I think the liability to some of the manufacturers is already there. Granted, parvovirus is not CJD but there are other pathogens that are already transmitted through factor.

DR. SCHONBERGER: Can we make it the sense of this Committee that we want to increase the flexibility of the FDA regulators to the extent possible to help them solve the day-to-day problems that they run into with regard to this issue? If they can make these kinds of exceptions or negotiate with industry, and so on, that --

DR. BROWN: I think what you are leading into is the possibility of what has been called the case by case analysis of the whole bundle. My guess is that "ain't" going to be popular.

DR. WOLFE: Good for question two.

DR. WHITE: I am not sure if this fits under what you are asking here, but I guess bovine proteins are used in

these products as well, and probably the Committee needs to be aware of the question of whether bovine proteins would come under this same sort of issue. That is, bovine serum is used in tissue culture. It is probably not an excipient -- excuse me, these are excipients; I will take it back.

DR. BROWN: I am so glad we don't have to get into a discussion of mad cow disease in the United States and the risks of American cattle to the human population via plasma products. That would be a bit much.

What I suggested, and if you disagree you can think of an alternative or just scrap it altogether -- my suggestion was that we exempt albumin from recall considerations with the exception of albumin used in vaccines for humans and albumin used in non-blood related products, for example recombinant products. In other words, you would not exempt albumin used in recombinant products from the recall; you would not exempt albumin used for vaccine from recall. But you would exempt albumin used for other uses, other excipients.

DR. DETWILER: And you think there is a difference in risk and that is why we are doing it for one and not another? For the albumin.

DR. BROWN: The vaccines were brought up by virtue of the sensitivity of the public and the parents of the

pediatric public in particular, and the recombinant simply because -- I hadn't thought of it but it was a good point, excipients can be used for recombinant products as well as stabilizers, stabilizers for synthetics. So there you have demonstrably no risk whatsoever and you are simply adding an unknown infinitesimal risk.

Anyway, that is what I would like to get your opinion on. Is everyone clear about what is being proposed? What is being proposed is another criterion appropriate to consider in deciding about recommending withdrawal is the criterion that albumin, with the exception of its use in vaccines or recombinant product stabilizers, should be exempt from recall consideration. Ray?

DR. ROOS: I like Larry's idea about trying to give FDA flexibility and I wondered whether you could make it more vague, Paul. There may be some benefits to saying that there may be certain excipients that aren't withdrawn depending on information concerning them.

The reason I say that is, number one, we provide perhaps some flexibility and, number two, the whole albumin story sounds like it is beginning to be a little bit like a jigsaw puzzle. You know, you can use it for A but not for B and so forth. And we are probably not thinking of a number of conditions that fall into one or another category.

In addition, you know, we are dealing with a small risk to begin with and I am not sure that smaller or smallest should make so much of a difference at this point.

DR. BROWN: Well, is your idea perhaps to say that the FDA should be allowed to consider albumin with leniency?

DR. ROOS: I would have said --

DR. BROWN: That is vague.

DR. ROOS: -- certain excipients. I would have said certain excipients and leave it at that, that there may be certain excipients that are in infinitesimal amounts as an excipient or under some situations in which it makes it acceptable. I would have rather left it vague rather than naming albumin.

DR. BROWN: Well, let's see what that give the FDA. It gives the FDA carte blanche on excipients, doesn't it? In other words, let the FDA decide, and all we are saying is we don't want to give you any direction in the decision but it is all up to you. I would prefer to give them as much direction as I could but we could vote on either one, if you would like a different question, which is to allow full discretion in making exceptions. I think that is what you are suggesting.

Does anybody have a different way to phrase these two possibilities? If not, we will go around the table on

each one unless I hear an objection. All right, let's go around the table on the second one first, which is Ray's suggestion that we recommend that the FDA be given complete flexibility, or any way you want to phrase it, in their judgment on what shall and shall not be exceptions.

DR. ROOS: We are talking about secondary products here with excipients, and also that this item be appropriately labeled, or we can talk about how to do that. In other words, perhaps we are going to put something on this product to designate it but maybe we are avoiding the withdrawal of it.

DR. BROWN: I don't think that we should combine these two things. I think that is a tag-on and it may be that would not be a good idea. But we are, again, specifically talking about a plasma derivative as an excipient, and your idea is that this should be a matter for the FDA to decide on, on a case by case basis.

DR. SIEGEL: Let me interject here in terms of framing the question. We have that flexibility. Of course, the advice of an advisory committee is advisory and we will be able to make, and are making, and will continue to make case by case decisions. However, what we are looking for here is expert assistance in making those. So, in a sense, the issue I hear being discussed is should we, in making

those decisions, consider factors such as that? Is it the sense of the Committee, for instance, that albumin carries substantially less risk and that should be an important factor to consider? Or, is it the sense of the Committee that use in vaccines or other non-blood products is an important factor that should be considered differently? I think that simply advice that we should make a case by case decision isn't going to get us very far.

DR. BROWN: Well, that is blown out of the water.

DR. ROOS: Go on with your albumin.

DR. BROWN: Is there anybody who would like to rephrase the albumin issue? I mean, just simply to say that we suggest to the FDA that albumin represents a particularly low risk excipient?

DR. HUESTON: Low hypothetical risk.

DR. BROWN: Yes. Everything is hypothetical. We haven't got any cases for anything.

DR. HUESTON: Exactly. I think you are closer there to a nice way to state it, which essentially is saying instead of making blanket that any plasma derivative should be considered at the same level and that the FDA should respond similarly, giving the impression that they are the same level of risk, in fact, we are acknowledging --

DR. BROWN: Okay, then we can say that the

Committee would like to convey to the FDA that it considers albumin as a particularly low risk excipient, and leave it at that.

DR. DETWILER: But, Paul, I think it is important though to put down not just low because then that will convey that we know there is, and I think it is important to put if there is any risk at all.

DR. BROWN: Low to zero? Low -- let's just get the right wording.

DR. DETWILER: Yes, because low conveys that there is some evidence that there is.

DR. BROWN: Okay, that implies that there is some risk.

DR. TRAMONT: Low, if any, risk.

DR. HUESTON: Can I give you a sound bite? I will give you a sound bite example, that if you are covering this somebody could take out a three-second sound bite earlier and say does that mean this Committee supports giving this dangerous substance to children? That was when we were talking about the vaccine. I think we need to put all of this into the context that there is no demonstrated risk and what we are talking about is managing a hypothetical, a theoretical risk. So in this case, if there is a risk, whatever that risk might be, the processing of albumin

reduces that by many, many orders of magnitude to a very low level, if it exists at all.

DR. BROWN: Any other suggestions for wording? I am not totally happy with that either.

DR. LESSIN: How about least possible?

DR. BROWN: It is sort of funny to say that we are putting a hierarchy on hypothetical risk.

(Laughter)

This is level two hypothetical risk.

DR. WHITE: I think so too, Paul. I think we are quibbling here. I think it either has a risk or it doesn't have a risk and we don't have the answer to that yet.

DR. TRAMONT: So why don't we say it? We don't know it. Can we say since we don't know if there is a risk or not we would recommend -- we would advise that albumin be exempt, or something like that?

DR. WHITE: Well, I think the members of the Committee should vote -- I mean, essentially their votes are going to say whether the risk that they perceive is an acceptable risk or not an acceptable risk. We all think the risk is exceedingly low. We are all probably very close to saying it can be excluded as a withdrawable product but we are not quite there yet. Probably by the time we get to the point where we would be there, albumin will no longer be

used as an excipient in some of these products. But the fact is that I think we are all seeing the same risk but we are responding a little bit differently. Some are willing to accept that risk perhaps and some are not. I would just vote on your question the way it is. I mean, I think that will be informative to the FDA. I think that will tell them the response of the Committee of the very low risk that we are all perceiving and they will get the message.

DR. BROWN: All right. We probably should take a five-minute recess and get the wording. That is what is done often, but I will just go ahead and barge on. The Committee acknowledges that all risk associated with excipient administration is hypothetical. Sense one. Sense two, of the excipients that are used in human medicine, albumin seems to us to have the lowest possible risk.

DR. WOLFE: Add hypothetical.

DR. BROWN: Add hypothetical again. So it tells the FDA that we think that all of these risks are hypothetical and that this is the least of the risk substances that we are considering.

DR. WOLFE: I am not sure that that gets the FDA anywhere because, I mean, the FDA probably knows that, that albumin is less dangerous from the experimental evidence.

DR. WHITE: I agree. Just say your first

sentence. Your first sentence everybody is going to agree on, and for your second sentence just say it has a low risk and then have people vote on whether or not they would exempt albumin from what we voted on the first time.

DR. HUESTON: From the automatic withdrawal.

DR. WHITE: Yes.

DR. BROWN: Let's do the very first proposal then, the one that I proposed first and if we don't agree, then we can go back. I proposed an exemption for albumin except as used in vaccines and non-plasma products. In other words, albumin exempt from the recall policy except in its use as an excipient for vaccines and non-blood based products. Linda?

DR. DETWILER: I am going to abstain on this because --

DR. BROWN: Abstain?

DR. DETWILER: Abstain.

DR. BROWN: Okay.

DR. DETWILER: I am troubled by differentiating the exceptions from the exception.

DR. BROWN: Okay, Ray?

DR. ROOS: Paul, just clarify for me for a second. I understand the vaccine issue but the recombinant one?

DR. BROWN: The idea was that we shouldn't add

albumin to a no-risk substance, a totally no-risk substance in the context of CJD, which is a recombinant Factor VIII for example.

DR. ROOS: Okay, yes, I agree with that.

DR. BROWN: Gil?

DR. WHITE: Well, I thought when you were getting ready to go around I was going to say no, that I wouldn't exempt albumin but I think the way you have worded it I would. My only message to the FDA is what I said to begin with, and that is that if you are adding albumin to a recombinant product you are adding a risk to something that didn't have a risk. I am very comfortable with albumin as an excipient in a plasma-derived product which already has a risk, and I don't see any reason to withdraw that plasma-derived product because of the albumin.

DR. BROWN: Right, and that is built into this proposal.

DR. WHITE: And that is what you are saying.

DR. BROWN: That is right.

DR. WHITE: So I think I agree with the way you worded it. That is what I am saying.

DR. BROWN: Barbara?

MS. HARRELL: I agree.

DR. BROWN: Ed?

DR. TRAMONT: Yes.

DR. BROWN: Leon?

MR. FAITEK: Yes.

DR. BROWN: Sydney?

DR. WOLFE: Yes.

DR. BROWN: I agree. Larry?

DR. LESSIN: I agree.

DR. BROWN: Lawrence?

DR. SCHONBERGER: I agree but --

DR. BROWN: Oh!

DR. SCHONBERGER: -- there is the issue of whether withdrawing it has any measurable benefit --

DR. BROWN: Yes, we all know that. Okay.

DR. SCHONBERGER: That is understood.

DR. BROWN: Yes. Bill?

DR. HUESTON: I agree.

DR. BROWN: A unique 100% concurrence with that suggestion and I think the FDA ought to know that we had difficulty in the wording of the exact suggestion but, certainly, the sense of this Committee is that the FDA should consider albumin as a good candidate for exemption from withdrawal as a minimum.

Question two, TSE-implicated plasma derivatives in manufacturing process reagents. When an FDA-regulated

plasma derivative has been withdrawn because a donor who contributed to the plasma pool was later diagnosed with CJD, or was determined to be at increased risk of TSE the safety of secondary FDA-regulated products manufactured by processes using the withdrawn plasma derivative as reagents is considered by reviewers on a case by case basis. Factors considered are described in the charge.

The example of this particular situation is the transferrin case I think. Just to refresh your memory, transferrin was processed from a pool of plasma to which a CJD donor had contributed. The transferrin was then used as a growth factor and tissue culture for the production of monoclonal antibodies, which were then put on an affinity column to purify Factor VIII and anti-hemophilic factor. The question then was do we withdraw the anti-hemophilic factor? So this is a very derivative product.

In that kind of a situation, the FDA currently has no blanket determining criterion. It determines each case individually. Is there any discussion about this before we answer or poll on the first question, which is, do the members of this Committee agree with this policy? Yes?

DR. WOLFE: This seems to me to be an entirely reasonable policy and the details range from situations where there isn't any of the substance there to ones where

there may be some there, and to discourage the FDA from considering it on a case by case basis would seem foolish. I would strongly support it and the details that we would have to offer would themselves have to be on a case by case basis. I don't know what we can say to elucidate FDA's case by case decision-making. So I would strongly agree with both of the questions.

DR. BROWN: As we have already heard, the FDA can do this anyway.

DR. WOLFE: Right.

DR. BROWN: They can do anything case by case.

DR. WOLFE: Right.

DR. BROWN: So we are not helping them at all by telling them we agree.

DR. WOLFE: Right.

DR. HUESTON: We are in the sense that if this group came back and said that there should be a blanket withdrawal, that would be important.

DR. WOLFE: We couldn't have any scientific basis for saying that though.

DR. HUESTON: That has not prevented advisory committees in the past from making recommendations.

DR. WOLFE: We are talking about our Advisory Committee, not others.

DR. BROWN: This is a whole new thing; this is our Advisory Committee. Well, shall we go ahead and poll?

DR. SIEGEL: Let me comment a bit on the intent of this question and how you can help us. I think it is self-evident that this is a broad spectrum of things and it has to be done on a case by case basis. I think you have the list, but we have listed the six factors that we use: the nature of the population to be treated, the potential dose of agent that is potentially in there, the amount of purification in the process, short supply issues and the route of administration.

The second part of this question is a "please comment." I think it is really how we should use those factors, which ones you think are more important, should we not worry? For example, what we are seeing a lot in the case of transferrin, which has impacted more on products in the experimental stage in addition to the one you heard of in the licensed product, is that the transferrin, through the various processing steps, may be removed by several logs. You know, we had one case where it was estimated that there was well under Avogadro's number, you know, so that there were probably not any molecules of transferrin left in the final product. But then the issue arises do we know that the TSE agent hasn't jumped from the transferrin to the

to the producing cells and from it to the monoclonal antibody, and then bound to the column and then jumped off that monoclonal antibody onto the final product. Suffice it to say, our decision in most of those cases has been, with consent, to allow experimentation to go on. However, there is a significant level of concern and we would appreciate commentary on to what extent our current knowledge can address those concerns and how we should deal with them.

DR. BROWN: Well, either you or Jay might be able to tell us the kinds of other situations that could occur.

DR. SIEGEL: What we have seen to date are --

DR. BROWN: Monoclonal antibody purifications. What other kinds of things?

DR. SIEGEL: Right, we have had monoclonal antibody purifications not only of proteins that have gone into humans, as was the case. We have had monoclonal antibodies that go directly into humans, such as a monoclonal antibody against an infectious agent. We have had monoclonal antibody purification of cellular therapies, a cell such as hematopoietic stem cell --

DR. BROWN: So generically we are talking about factors that would be used in tissue culture to produce monoclonal antibodies for whatever reason --

DR. SIEGEL: Right.

DR. BROWN: -- that would be one general situation.

DR. SIEGEL: Right, but there could also then be factors used to produce recombinant proteins. For example, in the cloning stage, particularly if you are using not bacteria but a eukaryotic process as a supplement to the medium, albumin or transferrin, to grow up either a master cell bank or a working cell bank. That might then be used to make a recombinant growth factor. That growth factor might either be administered to humans or used in further tissue culture for production of other products.

DR. BROWN: But, again, you have elaborated a number of examples of materials used in tissue culture fundamentally.

DR. SIEGEL: Yes, that is basically --

DR. BROWN: Culture ingredients.

DR. SIEGEL: And in this case we are talking about products that are subsequently, in most cases, relatively highly purified to the exclusion to at least the substance that was added, the plasma derivative that was added.

DR. EPSTEIN: Albumin is also commonly used to stabilize proteins during column purifications and is, we believe, removed in subsequent steps. But that would be dissimilar to a culture additive. It is directly added to

the end-processed product.

Albumin is also used in the preparation of many reproductive therapies, including cryo preservation of banked semen and embryos. Although there may be subsequent washing steps, those procedures would not have the same character of extensive chemical purification, as is the case for various purified monoclonal antibodies or other common proteins.

So I think there is a broader range of scenarios than culture additive. But let me also comment, and it comes back to an earlier point made by Dr. Roos, in the setting of investigational products we have the ability to deal with the specific information of a potential contamination and obtain an informed consent. When we are dealing with a product that is already licensed, on the market, the ability to inform the patient is itself a withdrawal action, or a market correction, or a recall. In other words, you can't get the word out there without doing some kind of notification process and that is fundamentally different.

So, Dr. Siegel gave many correct examples where we have been able to deal with the issue but we have been able to couple it with notification, and we don't have quite the same latitude with the already distributed product where, if

we seek specific labeling, it is likely to end up withdrawn and never be re-released.

There is also the legal problem that the FDA cannot mandate the specific risk label on theoretical grounds. If there is no actual evidence of a product risk, not known adverse reaction, we have a legal problem mandating that that risk be labeled, let alone for a particular lot. We have been having that debate with industry both at the level of specific lot labeling in cases of known donation from a donor at risk, but also in the case of generic labeling where the authority to mandate that has been contested.

DR. BROWN: Thanks.

DR. RICHMAN: If I could just add for the Office of Vaccines, we have had transferrin used experimentally in the cell culture fluid, and an issue has arisen where it wasn't discovered until after the product was already used and the study was long over that the transferrin lot was unsatisfactory with regard to the CJD status of the donors. Then the issue of disclosure, which is item 6 up there on the chart, is coming into the play. The company is discussing with the FDA what should be disclosed to patients, for example, who received this.

DR. BROWN: It just seems to me that we don't need

to talk about items 1, 4, 5 and 6. They are common to everything that you do. Everything. Our feeling, or at least my feeling about those factors is that they apply across the board. I think 2 and 3 are the crucial matters and they both have to do with dose. Certainly, the manufacturing process has to do with dose, and item 2 has to do with dose. That is basically, it seems to me, why you separated this from the excipients because the dose here is going to be even less than it is in an excipient. That is what primarily, it seems to me, is what distinguishes the products or the policy of question 2 from question 1. It is dose. And factors that relate to dose.

You want guidance. The Committee could decide that this level of dose is just beyond reason to include under any withdrawal policy. We can say that manufacturing process reagents -- you can just forget them. Or, we can say, no, we have to worry about them on a case by case basis. Committee? Leon?

MR. FAITEK: What was the resolution with the transferrin in the Factor VIII case? What was the decision on that?

DR. BROWN: The decision was, first of all, to allow the product to be used. I don't know about labeling or notification, or whatever, but there was a green light

given to that product.

DR. EPSTEIN: The decision was made to permit the product to be distributed without specific labeling. We did make the effort, however, to share with the affected community through activist organizations the decision-making process that had led to that conclusion, and the data on which the decision was based were shared with the hemophilia community.

MR. FAITEK: Was there any kind of agreement from the hemophilia community that was consulted? Did they concur in that decision?

DR. EPSTEIN: Yes. Of course, they were not concurring as part of any official process but they did indicate acceptance of it.

DR. ROOS: There may be some potential issues here with respect to some of the plasma products. For example, one could envision that somebody was going to get a transplant that was going to end up in the central nervous system that was going to be exposed to one product or another product. So I think there are certain situations that look to me to be pretty trivial because of the low dos and low exposure and route, and there are others which might involve, you know, what your cornea transplant is bathed in before it is implanted.

DR. BROWN: You know what the best example is? it has just occurred to me, is implanting a little piece of embryonic brain tissue into the brain of a patient with Parkinson's disease to alleviate the symptoms, which is now an experimental procedure. So that is the sort of thing you are talking about. If that piece of tissue that was embryonic were kept alive in tissue culture with an albumin as one of its macromolecular constituents, then you would have a situation --

DR. ROOS: Certainly route and tissue would be important. It sounds to me like case by case handling of this is appropriate. I don't know whether we have to go into the real fine details.

The one thing, and I don't know whether FDA wants us to get involved in it, is number 6 which turns out to be a bit of a dilemma for practitioners and hospitals. In other words, what do you tell people and when do you tell them, and so forth? We kind of battle this in my institution when FDA alerts us of a problem with a biological, and I don't know whether we should enter that path.

DR. BROWN: It is 4:20. Does the FDA really want guidance on disclosure?

DR. ASHER: We discussed the possibility and, with

the Office of Chief Counsel, decided that it was probably not possible to come to a decision in this particular Committee. It is a controversial issue. Dr. Roos has alluded to the problems. They are the same for the FDA as they are for everybody else. We generally favor disclosure but, of course, to disclose a remote and hypothetical risk of a terrible fatal disease where there is no treatment and no early diagnosis and no public health implication for contacts, it seems that you are not doing them any favor by telling them about such a risk. But we are not going to solve that today.

DR. BROWN: Of course, you can really say the same thing for growth hormone recipients.

DR. ASHER: No, there the risk is not remote and hypothetical.

DR. BROWN: Well -- okay.

DR. HUESTON: Paul, can I add one issue there for the factors? I think I would also add at some point on that list look at the source of the raw material that was used in the process. We had a bit of a discussion here about the difference between, for instance, commercial size of the pool. We talked about the source and the amount of information you have on the donors and some other issues. So if you are going to do a case by case evaluation, then

that is another factor that ought to be included in the list because there may be characteristics that would be applicable.

DR. BROWN: You mean in terms of someone at higher -- in other words, distinguishing, say, a CJD donor from someone judged to be at higher risk than normal of getting CJD, distinguishing between these two as an important criterion?

DR. WOLFE: That would just be part of the dose consideration.

DR. HUESTON: I am just talking about the list of the factors that would be considered in that case by case process by which you would look at these secondary uses. I would just add to the list the source of the raw material that led to this.

DR. BROWN: I don't think these factors are complete. It seems to me there are other things that were included on other pages of our descriptive material.

DR. SCHONBERGER: Yes, we have donor characteristics on page three listed.

DR. BROWN: Yes, let's all agree that an evaluation of the degree of hypothetical risk, whether it is hypothetical to 10(-3) or hypothetical to 10(-6) be considered by FDA.

DR. SCHONBERGER: A third point under 2, I think, covered the issue you were raising, Paul, the donor characteristics.

DR. BROWN: Right. Is that what you all understand by donor characteristics? Whether the donor had a dura or whether the donor actually had CJD, this sort of thing? So that is in there.

DR. ASHER: Yes, we recognize that you can draw a line between a donor recognized with CJD because now there is no question that somebody contributing to the pool came down with the disease, but we realize you can't draw the line between somebody at high risk and the normal population where it is almost certain that large pools will contain an implicated donor.

DR. BROWN: Shall we vote? The question is, do the members of the TSE Advisory Committee agree with the policy as outlined for these manufacturing reagents, which are judged according to these factors on a case by case basis? Linda?

DR. DETWILER: Yes.

DR. BROWN: Ray?

DR. ROOS: Yes.

DR. BROWN: Gil?

DR. WHITE: Yes.

DR. BROWN: Barbara?

MS. HARRELL: Yes.

DR. TRAMONT: Yes.

MR. FAITEK: Yes.

DR. WOLFE: Yes.

DR. LESSIN: Yes.

DR. SCHONBERGER: Yes.

DR. HUESTON: Yes.

DR. BROWN: And I also vote yes. I wouldn't ruin two consecutive consensus for all the tea in China!

So we did not redirect FDA policy on question number two, and on question number one we agree in general and add a special recommendation that albumin, except under certain circumstances be looked at with leniency.

Is there any further discussion or comments that anyone wishes to make, either the Committee or the FDA or the general public?

If not, the meeting is closed. Thank you all very much.

DR. FREAS: Thank you, Dr. Brown and thanks to all the Committee members and members of the audience.

(Whereupon, at 4:30 p.m., the Committee adjourned.)

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